AMERICAN JOURNAL

OF

DISEASES OF CHILDREN

EDITORIAL BOARD

FRANK SPOONER CHURCHILL, Chicago

L. EMMETT HOLT, New York City — DAVID M. COWIE, Ann Arbor, Mich.

JOHN LOVETT MORSE, Boston — EDWIN E. GRAHAM, Philadelphia

JOHN HOWLAND, Baltimore

VOLUME V

1913

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO, ILL.

CONTENTS OF VOLUME V

JANUARY, 1913. NUMBER 1

PAGE

THE COAGULATION TIME OF BLOOD IN INFANTS AND CHILDREN. HOWARD CHILDS CARPENTER, M.D., AND J. CLAXTON GITTINGS, M.D., PHILADELPHIA 1

AN EARLY CASE OF CHONDRODYSTROPHY WITH RADIOGRAM AND NECROPSY. L. E. LA FÉTRA, M.D., NEW YORK 18

METHODS OF ESTIMATING KIDNEY FUNCTION. RICHARD M. SMITH, M.D., BOSTON 25

THE VACCINE THERAPY OF WHOOPING-COUGH. ARRIE BAMBERGER, M.D., CHICAGO 33

FAT AND NITROGEN METABOLISM IN A CASE OF CONGENITAL ABSENCE OF THE BILE-DUCTS WITH A STUDY OF FERMENTS OF THE PANCREATIC SECRETION AND THE FECES. HENRY KOPLIK, M.D., AND BURRILL B. CROHN, M.D., NEW YORK 36

ACUTE LYMPHATIC LEUKEMIA IN EARLY LIFE. AUGUST STRAUCH, CHICAGO 43

ON THE CAUSE OF THE PERSISTENCE OF GONORRHEAL VULVOVAGINITIS IN CHILDREN. I. C. RUBIN, M.D., AND J. S. LEOPOLD, M. D., NEW YORK .. 58

A STUDY OF THE WASSERMANN REACTION IN CONNECTION WITH HEREDITARY SYPHILIS. L. R. DE BUYS, M.D., NEW ORLEANS 65

PROGRESS IN PEDIATRICS: PROGRESS OF OPHTHALMOLOGY WITH SPECIAL REFERENCE TO DISEASES OF THE EYE IN CHILDREN. HOWARD F. HANSELL, M.D., PHILADELPHIA 70

INDEX TO CURRENT PEDIATRIC LITERATURE 81

FEBRUARY, 1913. NUMBER 2

SURGERY OF THE THYMUS GLAND, THYMECTOMY. REPORT OF FIFTY OPERATED CASES. CHARLES A. PARKER, M.D., CHICAGO 89

ANGIOMA OF THE LARYNX, ESPECIALLY ITS RELATION TO CHRONIC LARYNGITIS; WITH REPORT OF A CASE IN A CHILD NINE MONTHS OLD, FOLLOWING MEASLES. REVIEW OF THE LITERATURE. JOHN PHILLIPS, M.B., AND H. O. RUH, M.D., CLEVELAND, O. 123

OSTEOGENESIS IMPERFECTA. REPORT OF A CASE WITH THE STUDY OF ITS METABOLISM. HERMAN SCHWARZ, M.D., AND MURRAY H. BASS, M.D., NEW YORK 131

CONGENITAL ATRESIA OF THE ESOPHAGUS, WITH REPORT OF THREE CASES. JOSEPH BRENNEMANN, M.D., CHICAGO 143

THE REDUCTION OF INFANT MORTALITY IN NEW YORK CITY. S. JOSEPHINE BAKER, M.D., NEW YORK 151

PROGRESS IN PEDIATRICS: RÉSUMÉ OF WORK ON TUBERCULOSIS IN CHILDREN FOR 1912, MAY MICHAEL, M.D., CHICAGO 162

INDEX TO CURRENT PEDIATRIC LITERATURE 197

MARCH, 1913. NUMBER 3

DIETETIC TREATMENT OF CONVULSIONS AND ALLIED CONDITIONS OCCURRING IN INFANCY. CLIFFORD G. GRULEE, M.D., CHICAGO 205

THE SIGNIFICANCE OF THE PYLORIC REFLEX IN TRUE AND PSEUDOPYLORIC STENOSIS IN INFANTS. DAVID MURRAY COWIE, M.D., ANN ARBOR, MICH. 225

290179

PAGE

STATISTICAL COMPARISON OF THE MORTALITY OF BREAST-FED AND BOTTLE-FED INFANTS. WILLIAM H. DAVIS, M.D., BOSTON 234

VULVOVAGINITIS IN CHILDREN. EDITH ROGERS SPAULDING, M.D., BOSTON ... 248

THE PANCREATIC FERMENTS IN INFANTS. II. IN ACUTE INTESTINAL INDIGESTION (ALIMENTARY INTOXICATION). ALFRED F. HESS, M.D., NEW YORK .. 268

PROGRESS IN PEDIATRICS: RECENT CONTRIBUTIONS TO THE STUDY OF PYELITIS IN INFANCY. RICHARD M. SMITH, M.D., BOSTON 273

INDEX TO CURRENT PEDIATRIC LITERATURE 279

APRIL, 1913. NUMBER 4

A STUDY OF MERORACHISCHISIS (SPINA BIFIDA OCCULTA). BARNET JOSEPH, M.D., BURLINGTON, VT. 285

PROTEIN MILK AS A CORRECTIVE OF DIGESTIVE DISTURBANCES. HERBERT B. WILCOX, M.D., AND MINER C. HILL, M.D., NEW YORK, WITH OBSERVATIONS, ETC. BY B. RAYMOND HOOBLER, M.D., NEW YORK 297

PROTEIN METABOLISM IN INFANTS FED ON PROTEIN MILK. B. RAYMOND HOOBLER, M.D., NEW YORK 308

THE COMPLEMENT FIXATION TEST IN THE MANAGEMENT OF GONOCOCCUS VULVOVAGINITIS. GEORGE G. SMITH, M.D., BOSTON 313

DIPHTHERIA SEPTICEMIA, WITH REPORT OF A CASE. EDWARD MORGAN, M.B., NEW YORK 317

PROGRESS IN PEDIATRICS: A REVIEW OF SOME RECENT PUBLICATIONS ON ANATOMY AND PATHOLOGY. G. M. SMITH, M.D., ST. LOUIS 322

INDEX TO CURRENT PEDIATRIC LITERATURE 335

MAY, 1913. NUMBER 5

GASTRIC MOTILITY IN INFANTS AS SHOWN BY THE ROENTGEN RAY. MAYNARD LADD, M.D., BOSTON, MASS. 345

REPORT OF A CASE OF AMYOTONIA CONGENITA (MYATONIA CONGENITA-OPPENHEIM) WITH AUTOPSY. NATHAN CHANDLER FOOT, M.D., CHESTNUT HILL, MASS. 359

A CASE OF CONGENITAL MYXOMA OF THE FEET. MEILO LEITAO, M.D., RIO DE JANEIRO, BRAZIL 374

THE VACCINE TREATMENT OF WHOOPING-COUGH. E. MATHER SILL, M.D., NEW YORK 379

METABOLISM OF A CHILD WITH COMPLETE ABSENCE OF THE BILE FROM THE INTESTINES. WILLARD S. PARKER, M.D., BOSTON 386

THE SCIENTIFIC BASIS FOR THE ARTIFICIAL FEEDING OF INFANTS. JOHN HOWLAND, M.D., BALTIMORE 390

INDEX TO CURRENT PEDIATRIC LITERATURE 415

CONFERENCE ON INFANT MORTALITY 424

JUNE, 1913. NUMBER 6

INFANTILE CEREBRO-CEREBELLAR DIPLEGIA, OF FLACCID, ATONICASTACIC TYPE. L. PIERCE CLARK, M.D., NEW YORK 425

PAPULO-NECROTIC TUBERCULIDES IN INFANTS. BENNO M. WRONKER, A.B., M.D., NEW YORK 447

THE PATHOGENESIS OF CASEIN CURDS IN THE STOOLS OF INFANTS. ALFRED F. HESS, M.D., NEW YORK 457

THE DIAGNOSTIC VALUE OF THE V. PIRQUET TEST. F. L. WACHENHEIM, M.D., NEW YORK 466

SEVENTIETH ANNIVERSARY OF ADOLPH BAGINSKY. LOUIS FISCHER, M.D., NEW YORK 468

PROGRESS IN PEDIATRICS: RÉSUMÉ OF THE LITERATURE ON INFANT FEEDING AND DISEASES OF THE DIGESTIVE SYSTEM, FROM JULY, 1912, TO MARCH, 1913. MAURICE OSTHEIMER, M.D., PHILADELPHIA 469

INDEX TO CURRENT PEDIATRIC LITERATURE 488

AMERICAN PEDIATRIC SOCIETY 499

ENGLISH CONFERENCE ON INFANT MORTALITY 500

American Journal of Diseases of Children

Vol. 5 JANUARY, 1913 No. 1

THE COAGULATION TIME OF BLOOD IN INFANTS AND CHILDREN *

HOWARD CHILDS CARPENTER, M.D., AND J. CLAXTON GITTINGS, M.D.
PHILADELPHIA

The value of a reliable yet practicable method for the determination of the coagulation time of blood is obvious, yet the amount of experimental work expended on it within recent years testifies to the difficulties inherent to most of the clinical methods which have been devised.

The large majority of observations, however, have been made on adults, so that it seems desirable to extend the study to infants and children, both in health and disease, in order to decide, if possible, on a standard for comparison.

Before presenting the conclusions of other authors and the results of our own work, we may consider briefly the various coagulometers in use, with an equally brief discussion of the most important and established factors of error more or less inherent to any clinical method.

A recent article by Myer Solis-Cohen contains such a thorough consideration of instruments and methods that it would appear to be a work of supererogation to present another résumé. We may take this opportunity of acknowledging our indebtedness to him, both for the collaboration of the results, and for his extensive and complete bibliography which brings the literature of clinical methods up to a recent date.

According to Solis-Cohen, these methods may be divided into classes, according to the principles employed. We have rearranged his classification as follows:

1. Methods in which the blood is drawn into capillary tubes.
2. Methods in which the corpuscles are set in motion by a current of air or oil directed against the drop.
3. Methods in which the blood is collected on one or more wire loops.
4. Coagulation time determined by formation of film.
5. Coagulation time determined by observing changes in contour of drop.

---

*Read at the meeting of the American Pediatric Society, Hot Springs, Va., May, 1912.

6. More or less complex methods, necessitating the employment of activated serum, anticoagulant substances, etc.

With such a diversity in technic, it is plain that each individual method in the various classes must be interpreted in terms of its own normal time limit for coagulation, to which must be added the variation dependent on the personal equation of the investigator who employs it.

For example, the accompanying table (Table 1) compiled by Solis-Cohen, emphasizes the truth of this statement.

TABLE 1.—NORMAL CLOTTING-TIMES OBTAINED WITH DIFFERENT METHODS

Method Employed	Clotting-Time Obtained, Minutes
Class I—	
Vierordt's	9½
Wright's	2½ to 5
McGowan's	8
Addis' modification of McGowan's	9½
Rudolf's modification of McGowan's	8½
Sabrazés'	9 to 10
Schultz's	5
Class II—	
Brodie-Russell	3 to 8
Pratt-Grützner modification of Brodie-Russell	3 to 8
Bogg's modification of Brodie-Russell	3 to 8
Addis' modification of Brodie-Russell	8
Class III—	
Biffi's	7 to 10
Goldhorn's modification of Biffi's, about twice as long as above	
Buckmaster's	5¾
Class IV—	
Slide and Straw	2½ to 5
Schwab's	4¾ to 5½
Bürker's	6 to 7
Riebe's modification of Bürker's	12 to 14
Class V—	
Hayem's	3 to 20
Milian's	15 to 34
Bezançon and Labbé's modification of Milian's	10
Hinman and Sladen's modification of Milian's	5 to 8
Duke's modification of Milian's	5 to 7
Solis-Cohen's modification of Milian's	8⅔
Class VI—	
Morawitz's	5

It is evident that many factors are concerned in the production of such wide variance in results. The most important of these may be considered briefly.

CONTACT WITH A FOREIGN BODY

It has long been recognized that coagulation of blood is hastened by contact with any foreign body other than a pure oil or paraffin. With proper precautions to exclude these foreign factors, including air, the coagulation time can be immensely lengthened. In the use of clinical methods it is clearly impossible to exclude them. In the hands of a

practiced operator, however, these errors should be approximately the same for each method. The variable factors over which we can exert no control are the atmospheric conditions and the viscosity of the blood. The other factors, which may be variable in the case of the novice, but which are obviated largely by the skill resulting from constant practice, are, (1) presence of dirt on the site of puncture or on the instrument; (2) pressure on the tissues surrounding the puncture; (3) depth and width of the puncture with their influence on rapidity and volume of the flow; (4) amount of blood withdrawn; (5) length of time in which the blood remains in contact with the tissues; (6) the temperature at which the blood is allowed to coagulate; (7) the shape, diameter and depth of the drop under observation; (8) end point adopted.

The last three factors vary according to the method employed, as well as with the skill of the operator. It is altogether probable that other factors exist of which we have no accurate knowledge. The foregoing list contains the chief sources of error which affect the clinical methods now in use.

Granting that the site of puncture and the instrument shall be absolutely clean, that the puncture shall be deep and wide enough to permit of free and rapid flow and that no pressure shall be made on surrounding tissues, we may consider the remaining factors.

The influence exerted by the amount of blood withdrawn is obviously connected with the well known fact that the coagulation time lessens, the longer the flow of blood. Of equal and similar importance is the influence of contact with the tissues—the longer the contact the shorter the time required for coagulation.

The remaining factors are inherent to individual methods. The concensus of opinion indicates that the effect of temperature is of extreme importance, heat hastening and cold retarding coagulation time. The necessity of making provision for the maintenance of body temperature during the time the blood is under observation seems to us so obvious that we have employed none of the simple but inaccurate methods by which the blood is exposed to the varying temperatures of the room.

The importance of the size and depth of the drop has been emphasized, but, we think, insufficiently. A further consideration of this may be postponed.

That the end-point adopted for the different methods by various operators must affect the published reports likewise is obvious. In general, it may be said that the method which permits of the easiest and least disputable interpretation, possesses the greatest practical advantage.

It would be of advantage to consider at greater length those factors which exert the greatest influence on the coagulation time of blood with whatever method observed, namely, the amount of blood withdrawn and

the duration of its contact with the tissues. These depend on the intrinsic phenomena of coagulation *per se,* and, therefore, are inseparably connected with the method of securing blood by puncture of the skin.

From the chaos of ideas produced by the vast amount of experimental work on the problem of the coagulation of blood, a fairly clean cut theory has been evolved, due principally to the studies of Morawitz and Fuld, and Mellanby. It may be stated as follows:

The factors essential to coagulation are the following:

1. Fibrinogen, one of the component parts of blood, belonging to the group of globulins.

2. Prothrombin, also present in the blood, but of unknown chemical composition. It exists in a condition of absorption in the fibrinogen molecule (Addis).

3. Ionizable calcium salts, present in the blood.

4. Antithrombin, a hypothetical substance which exists in the circulating blood. It is probable that its counterpart exists in the antithrombin which has been isolated in approximately pure form from the salivary glands of the leech. This is a soluble protein resembling the peptones and proteoses (Howell). Certain it is that a substance with antithrombic characteristics is found in "peptonized blood."

5. Finally, there is a substance known as thrombokinase (thromboplastin), of unknown chemical composition, which is present in all the body tissues, especially those rich in nucleoprotein, and in the formed elements of the blood (platelets), but is not found free in the circulating blood.

The first four substances are supposed to be present in normal circulating blood at all times. The last, kinase, appears when there is injury to body tissues or to formed elements of the blood.

According to the theory we are discussing, when prothrombin and thrombokinase come into contact in the presence of ionizable calcium salts, there is formed, after a short interval, a substance known as thrombin, which unites instantly with fibrinogen to form fibrin — the substructure of the blood-clot. From its power to prevent the formation of this substance, thrombin, the so-called antithrombin gets its name.

According to Addis, on account of the close molecular relation which exists between this newly-formed thrombin and fibrinogen, the thrombin escapes the neutralizing action of antithrombin, and fibrin is quickly formed from its action on the fibrinogen. "Most of the thrombin is precipitated with the fibrin. . . . That part of the thrombin which is not so precipitated is gradually neutralized by the antithrombin." As Mellanby points out, "The whole mechanism of coagulation is admirably adapted to produce large and rapid clotting within a wounded area, but

to stop the process immediately beyond the confines of the injured tissues" (by means of the antithrombin).

Since injury to the tissues by puncture at once makes the thrombokinase available, it is easy to see the importance of the above-mentioned factors of error in clinical determinations. The longer the blood flows and the longer the individual drop remains in contact with the tissues, the greater the amount of kinase and the more copious and rapid the production of thrombin, with the consequent shortening of the coagulation time.

On the basis of this simplified theory, Addis constructs a most plausible hypothetical explanation for the hitherto baffling phenomena of the slow or imperfect coagulation seen in the subjects of hemophilia.

Quite recently the work of Howell has cast justifiable doubt on the acceptance of the conclusions of Morawitz and Mellanby.

Howell's theory rests on two facts. "First, the presence in the circulating blood of a constant amount of antithrombin; secondly, the proof that this antithrombin is antagonized or neutralized by the thromboplastic substance (thrombokinase) which is found in tissue extracts."

According to Howell,

> **We may believe that circulating blood contains normally all the necessary factors for coagulation, namely, the fibrinogen, the prothrombin, and the calcium, but these factors are prevented from reacting, that is to say, the calcium is prevented from activating the prothrombin by the presence of antithrombin, which is also a constituent of the circulating blood. When blood is shed this antithrombin is neutralized by the thromboplastic substance (thrombokinase) furnished by the wounded tissues and the disintegrating platelets.**

In this theory we find an altered conception of the functions of thrombokinase and increased importance is given to the amount and activity of antithrombin. The sole function of the kinase lies in its power to neutralize antithrombin and thus permit calcium and prothrombin to form thrombin. The conception of the action of thrombin on the fibrinogen to form fibrin, remains unchanged. The source of thrombokinase in tissues and blood likewise remains undisputed.

A discussion of the merits of these two theories would serve no useful purpose. They are presented in order to convey the more recent views on this important and complex problem of blood coagulation. There are methods at present available for isolating four of these substances, fibrinogen, thrombin, antithrombin and thrombokinase. The study of the individual case of deficient coagulation according to more advanced standards must be pursued along these lines. Deficiency of one or more of these substances can be inferred, if not always definitely proved, by such studies as those of Whipple, and Schloss and Commiskey in cases of hemorrhagic disease in the new-born. Nevertheless, it seems important to decide how far the clinical method in the hands of the practitioner

unskilled in advanced technic, can be trusted to establish the presence or absence of a delayed coagulation time, and to compare results in the young with those in the full-grown.

Whether we accept the action of the thrombokinase of the injured tissues, as an activator of prothombin and calcium, or as a neutralizing agent for antithrombin, does not affect the clinical method *per se,* since, in either case, excess of the kinase in the shed blood due to faulty technic in collecting the sample of blood will shorten the coagulation time.

CLINICAL METHODS

We must consider next the clinical methods which we have employed in the examination of our cases and the reasons for their selection.

Excluding all those methods which fail to make provision for maintaining bodily temperature, the essential qualifications seemed to be: (1) ease and rapidity of technic; (2) ease of determining the end-point; (3) uniformity in the size and depth of the drop.

For ease and rapidity of technic two types of methods present manifest advantages—those in which the drops of blood are collected on a smooth flat surface of glass, and those in which they are collected on platinum wire loops.

Of the methods in which the blood is collected on glass, that of Brodie-Russell and of some modification of Milian's use of the glass slide seem to have the most adherents. The principle of the Brodie-Russell method depends on the visible motion of the blood corpuscles, impelled by a current of air from compression of a rubber bulb. This technic introduces manifest and variable sources of error.

Probably the most reliable clinical method which has been devised is that of Addis, in which he substitutes for intermittent jets of air at variable temperature, a continuous stream of filtered mineral oil at constant temperature. The apparatus for this method presents the disadvantage of expense, while facility in operating it requires practiced skill somewhat above the average.

We have confined ourselves to the use of the Solis-Cohen modification of Milian's method and to the wire-loop method of Biffi. The latter permits of obtaining greater uniformity in the size and depth of the drops, while the former may possess some advantages over the loop method in determining the end-point.

In Solis-Cohen's method, four drops of blood, from 5 to 7 mm. in diameter, are collected on the lid of a Stender-dish, and the dish at once applied to the cover (the edge having been smeared with petroleum previous to the test). The cover, being held tightly in place with a broad elastic band, is immersed in a bath of water in a small open pan, kept at constant temperature (98 F.). At intervals the dish is removed from the water-bath and the drops inspected without removing the lid. Coagulation is considered to be complete when the profile of the drops

does not change as the dish is tipped vertically and when the drops show an evenly distributed density by transmitted light. (For full description see original article.)

In the hands of Solis-Cohen, this method gives an average clotting time for adults' blood of 8⅔ minutes.

With a little practice the method affords an easy and rapidly executed determination, and, in so far, seems to be free from criticism. Its disadvantage lies in the fact that there is not even approximate uniformity in the diameter and especially the depth of the drops. It is not feasible accurately to time and observe the clotting of more than four drops during one test. Among these four, the disparity in size may be quite marked. Although Solis-Cohen concludes that drops of a diameter between 4 and 7 mm. clot with equal rapidity, we have been unable to confirm his findings.

For this reason we have had constructed four smooth glass disks 5 mm. in diameter, which were cemented to the lid of the stender dish. The drops were then collected on these disks, which insured reasonable uniformity in the diameter of each. This method, being an adaptation of Duke's technic, we called the Solis-Cohen-Duke.

In spite of the uniformity in diameter, however, it was found to be impossible to secure drops of equal depth. The importance of the depth in determining the rapidity of clotting may be seen from the following:

Average coagulation-time of drops in 29 tests: Deep, 13.5 minutes; medium deep, 10.3 minutes; shallow, 6.5 minutes.

The clotting time for one drop, so large as barely to adhere to the disk, was twenty-one minutes (not included in making the averages above).

In both the original and modified Solis-Cohen methods, the chief inherent factors of error will be found, therefore, in the size and depth of the drops, and, although practice may minimize the error, it seemed desirable to avoid it.

With this difficulty emphasized, the method of collecting blood on fine wire loops of uniform size fastened to a wire stem offered distinct advantages.

The chief objection which has been raised to this method originated by Biffi, is that contact of the blood with the wire loops hastens coagulation and that fibrin is attracted by capillarity to the point at which the loop touches the stem.

In his use of the instrument, Addis found that whenever the wire touched the water the blood in all the loops became diluted. In the apparatus which we used (see below) this difficulty was never encountered.

It has been claimed, also, that the loops are not so easily cleansed as glass. This is clearly unwarranted, since heating in the live flame is an ideal method of securing absolute cleanliness.

The original instrument used by Biffi consisted of a glass jar with a cork perforated for the passage of the fine platinum rod with its five loops attached, and for a thermometer. The latter registered the temperature of water contained in the lower part of the jar. When the loops are filled with blood the rod is passed at once through the cork into the warm moist chamber over the water. At stated intervals the rod is pushed down until one after the other of the loops is introduced into the water. Coagulation is complete when the blood remains on the loop instead of being diffused into the water.

From the theoretical standpoint, it would seem that coagulation would be hastened by contact with wire. Reference to Solis-Cohen's table, however, shows that the clotting time by Biffi's method is from seven to ten minutes, which is a fair average of all the methods and distinctly longer than is obtained with the use of capillary tubes. The maximum-minimum range also is not so great as is seen in other methods.

Finally, it must be noted that the results with the Biffi instrument should be as uniform as those with any other, and permit, therefore, of a fair comparison.

In using the original instrument, difficulty was encountered in maintaining the proper temperature owing to radiation through the glass. In order to correct this defect, Brooks modified the instrument without altering the principle.

DESCRIPTION AND TECHNIC

The Biffi-Brooks coagulometer (Figure 1) consists of a movable glass tube 2.5 cm. in diameter, set in an oblong metal water-jacket, which surrounds three-quarters of the circumference of the tube. The metal cap of the glass tube contains two openings, one for a thermometer, the other for a metal rod on which is fitted a platinum wire 6 cm. in length. Beginning at the distal end of this single wire, four circular loops are made, 6 mm. apart, each 3 mm. in diameter.

We have added to the instrument a collar on which the metal cap of the glass tube lightly rests, facilitating its removal. Originally the caps fitted the tube so tightly as to make its removal too difficult for delicate work. We also replaced the screw-cap of the water-jacket with a thermometer, held in position by a rubber washer, thereby securing better control of the temperature in the water-jacket. Finally, we covered the water-jacket on three sides and bottom with asbestos, to prevent too rapid heat radiation.

In using the apparatus the water jacket is filled with water at 98 to 100 F. and the glass tube is slightly less than half filled with water at 98 to 99 F., which temperature must be maintained throughout each examination.

In perfecting our technic with the Biffi-Brooks instrument, much time was spent and many examinations were made which cannot be included in the tabulated results.

We finally selected the following course of procedure: The blood was obtained from a finger, since it was found to be much easier to control than any other locality. First, the wire loops were cleaned in the flame of an alcohol lamp. The

skin of the finger was washed with tincture of green soap and distilled water and then with 95 per cent. alcohol. Puncture was made deep enough to permit the free flow of blood. The first drop was wiped off with a dry cotton pledget, and then the distal loop filled from the second drop, care being taken not to touch the skin. The excess blood was then wiped off, and the second loop filled from the third drop; the third loop from the fourth drop, etc. The only variable factor is the thickness of the film of blood in each loop. Since small drops permit of securing too thin a film, care should be taken to secure a large free-flowing drop.

When all the loops were filled, the rod was at once introduced into the warm air chamber above the water in the glass tube. Within a definite time after the puncture of the skin—usually four to five minutes—the rod was gently lowered until the distal loop entered the water. Coagulation was considered to be complete only when the structure of the clot within the loop remained intact. It frequently happened that a very small amount of pigment would dissolve out of the coagulum.

There seems to be slight doubt that such solution of a minimal amount of pigment could not be interpreted as incomplete clotting so long as the loop was completely filled by a firm fibrinous clot. We have regarded such cases as "positive," therefore, in tabulating our results.

In a private communication from Harlow Brooks, he states that he has been accustomed to accept the appearance of fibrin shreds within the loop as an indication of coagulation. Such an assumption seems to us hardly justified since the presence of a small amount of fibrin by no means insures that firm and definite clotting has occurred. On the other hand, a clot in the loops, of toughness sufficient to withstand the solvent action of water, must give evidence of an ample supply of all the factors concerned in clot formation. For example, it has been shown that the clotting-time in certain cases of purpura may be within normal limits although the clot itself is soft and gelatinous, without tendency to contract. This condition has been supposed to be due to deficiency in one of the before-mentioned elements, possibly the prothrombin. It would seem to us, therefore, that the test as we have accepted it, furnishes a clue not only to coagulation *per se*, but also to the integrity of the resulting coagulum.

It is only fair to state, however, that we found certain discrepancies, the explanation of which is not certain. They can be shown in the following classification:

Coagulation complete in distal loop, not in the others, at same time, 6 examinations.

Coagulation greater in distal loop than in any others, at same time, 11 examinations.

Coagulation greater in first and second loops than in any others, at same time, 2 examinations.

Coagulation greater in first, second and third than in fourth at same time, 1 examination.

Coagulation incomplete in first, third and fourth, but complete in second at same time, 3 examinations.

In another case the third loop failed to show as much coagulation as the second at the same time.

Such inconsistencies probably depend on several factors.

It would seem to us that proximity of the blood to the warm water in the glass tube probably plays the most important rôle.

At the beginning of our work, when we were experimenting with technic, we found, in filling the proximal loop first, a number of instances in which the *distal* loop, nearest the water, showed the most advanced coagulation. Another factor is the possible variation in the thickness of the film of blood in the different loops. Of least importance, probably, is the factor of time — the distal loop being the first one to be filled.

The premature coagulation in the distal loop is less of an objection than may be supposed, because this loop is usually sacrificed in order to determine how rapidly coagulation is proceeding. When the first loop is found to be firmly coagulated the next loop is introduced at once, and the further procedure is determined by the effect of the water on the blood in it.

Two other objections, however, can be found against the instrument which are more serious.

The chief difficulty encountered is the inability to determine the end-point at every observation. All of the loops may be lowered into the water without the completion of coagulation in the last, thereby necessitating a second puncture. This is a more or less serious objection in the case of a struggling child. With increasing familiarity with the appearance of each loop as it was immersed, the number of failures to allow time for complete coagulation grew less, so that we determined to continue the use of the instrument because of its manifest advantages in securing greater uniformity in size of the drops and because of the ease and rapidity of technic.

The second objection is that four loops do not permit of frequent tests for coagulation and the time must often be reckoned in minutes instead of half and quarter minutes.

With practice, however, one learns to judge quite accurately from the behavior of the blood in one loop when to introduce the next. A five-loop rod, such as Biffi advised, would also increase the scope of the instrument. Finally, it is questionable whether shorter intervals than one minute offer any advantage in procedures which are more or less inaccurate, as are all of these clinical methods.

Our clinical material has been drawn from the Children's Departments of the Philadelphia General, University and Presbyterian hospitals and the Children's Hospital.

We have made 192 examinations of 176 patients. Of these, eighteen examinations of sixteen patients gave an undetermined coagulation time, and re-examinations could not be made. (In ten other examinations coagulation time could not be determined at first, but re-examinations

gave positive results. Only the positive results, therefore, have been considered in our tables.)

Of the 160 patients who gave a positive coagulation time, thirty-five were healthy, without ascertainable disease, except such affections as ring-worm of the scalp and scabies (eight cases); 125 patients suffered from a variety of diseases which will be detailed later. Grouping all the healthy cases and all those suffering from disease, we find the following averages:

Healthy Cases: Average coagulation time, 39 examinations, 9.4 min. (5-14 min.).

Cases not Healthy: Average coagulation time, 135 examinations, 9.7 min. (5-16 min.).

This shows an unimportant difference between the well and sick.

It is obvious that the cases which failed to give positive results are difficult to interpret. It is also obvious that they should not be excluded, and that any series in which one or more of them occur cannot be considered conclusive.

In order to make some use of them we have made the following calculations:

In eighteen examinations of sixteen patients, complete coagulation did not occur within an average time of 10.9 minutes.

Grouping the positive cases, both healthy and diseased, we find that 160 patients give an average coagulation time of 9.6 minutes (174 examinations).

Since the positive cases (160) exceed the undetermined cases (sixteen), as 10 is to 1, and the average coagulation time of the latter certainly exceeds that of the former by at least 1.3 minutes (80 seconds) —(10.9 to 9.6 minutes)—it will be seen that the average of positive cases should be increased by a minimum of one-eleventh of the difference between positive and negative. This would be approximately seven seconds or .13 of a minute.

Since we cannot tell how much more than the minimum should be added, we may express the combined figures with a plus sign, thus:

Blood of 176 patients gave an average coagulation time of 9.73 minutes + (192 examinations).

Although even by this calculation, the results cannot be considered accurate the error must be slight since we found, in the ten "negative" cases which were re-examined, the positive time for coagulation as often less, as it was greater, than the "negative" time. In other words, the blood which failed to coagulate within twelve minutes one day, might show a positive result in eleven minutes or thirteen minutes the next day.

In order to compare the results of tests made by the Biffi-Brooks method with those which we obtained by the Solis-Cohen method, the following figures are presented:

Solis-Cohen Method: Forty-one cases gave an average coagulation time of 7.6 minutes (5-11) (fifty examinations).

The shorter time observed in the Solis-Cohen method is easily accounted for by the more stringent proof of coagulation which is demanded in the Biffi-Brooks method, and would seem to dispose of the claim that the use of wire-loops materially hastens coagulation.

In order to determine the influence of other factors on the coagulation time, we made further subdivisions of our cases tested by the Biffi-Brooks method. Since we found no material difference in total averages between well and sick children, we can disregard the influence of disease in formulating the accompanying tables:

TABLE 2.—COAGULATION TIME, CONSIDERING AGE, SEX AND COLOR

	Time		Results — Positive	Results — Negative
Age—				
From birth to 2 years	9.0 min.	+	34	2
Third to seventh years inclusive	9.8 min.	+	68	16
Eighth to fifteenth years inclusive	10.3 min.		72	..
Sex—				
Males gave an average coagulation time of	8.5 min.	+	102	10
Females gave an average coagulation time	9.7 min.	+	72	8
Color—				
White children gave an average coagulation time of	9.1 min.	+	142	11
Colored children gave an average coagulation time of	9.7 min.	+	32	7

The figures for age will be discussed later. Those for sex show a greater difference than is found by Rudolf, who gives 7.76 minutes and 7.54 minutes, respectively, for males and females.

According to our results, there is no noticeable difference between the white and colored races in the early years of life.

We have made no attempt to determine those differences which depend on the time of day, according to the published reports of other observers.

In view of the great variations found in the blood of the same patient within a few minutes, it seems to us that the limitations of the clinical method would preclude the possibility of drawing trustworthy conclusions on this point. For the same reasons the influence of the ingestion of food or fluids, of exercise and of fever on coagulation time have been disregarded.

As has been said, we have had no case of hemorrhagic disease to examine other than that of scurvy. Likewise cases of hemorrhage, urticaria, severe anemia, leukemia, etc., have not been observed in our series.

There remains, therefore, the consideration of the effect of a variety of diseases on coagulation time (Table 3).

TABLE 3.—SHOWING EFFECT OF A VARIETY OF DISEASES ON COAGULATION TIME

DISEASES IN WHICH POSITIVE DETERMINATIONS WERE OBTAINED

Disease	Cases	Number of Examinations	Average Coagulation Time, Minutes	Minimum and Maximum, Minutes
Rubella (eruptive stage)	3	3	11.3	8 -16
Pertussis (paroxysmal stage)	3	4	9.4	6.5-13
Typhoid fever (febrile stage, one in relapse)	3	4	8.9	7 -11
Syphilis (hereditary)	4	4	8.9	7 -11
Chorea (one acute, two convalescing)	3	3	12.0	10 -14
Vaginitis (acute)	3	3	9.6	6 -13
Valvular heart disease (afebrile compensated)	5	5	8.4	5 -14
Infantile paralysis (chronic stage)	5	5	8.6	7 -11
Bronchitis (acute or subacute)	4	4	9.1	6 -11
Bronchopneumonia (uncomplicated) (4 acute, 7 convalescing cases)	11	11	8.9	6 -12
Bronchopneumonia (complicated) (acute stage) Four cases occurred with measles, and one with varicella. Since these diseases show a lengthened coagulation time they may be grouped	5	6	10.5	9 -12
Bronchopneumonia (complicated) (acute stage) Two cases occurred with pertussis, one with typhoid and one with vaginitis. Since these diseases show a normal coagulation time they may be grouped	4	4	8.0	5 -10
Combining all the results in bronchopneumonia, we find	20	21	9.2	5 -12
Tuberculosis,* Class 1: 11 active, 8 quiescent	19	22	11.5	9 -14

*We have divided the cases of tuberculosis into two classes: (1) Tuberculosis of the bones, joints, glands or skin, and (2) tuberculosis of the lungs, peritoneum, kidney, or general. Only those cases were included in which a diagnosis was absolutely justified. Several of the cases of rickets probably belong to this class, but the diagnosis could not be definitely established. Tuberculosis cases (Class 2) and certain other diseases containing some negative results are grouped together later.

INDIVIDUAL CASES OF VARIOUS OTHER DISEASES

Cerebrospinal meningitis (height of the disease)	1	..	5.0	.... ..
Scurvy (postorbital hemorrhage) (infant 10 months old)	1	2	5.75	5 5- 6
Nephritis with ascites	1	..	15.0	.....
Cretinism (taking thyroid extract for 6 years more or less continuously)	1	..	6.5	.....
Erysipelas	..	..	9.0	.....
Metastatic abscess	..	..	8.0	.....
Epiphysitis	..	..	6.5	.....
Cervical adenitis	..	..	9.0	.....
Cystitis	..	..	10.0	.....
Favus	..	..	10.0	.....
Empyema (2 examinations)	..	..	14.5	.....
Cerebral paralysis of arm	..	..	13.0	.....
Multiple neuritis	..	..	13.0	.....
Club-foot (much crippled)	..	..	12.5	.....
Congenital dislocation of hips (in bed)	..	..	12.5	.....

CASES GIVING BOTH POSITIVE AND NEGATIVE RESULTS

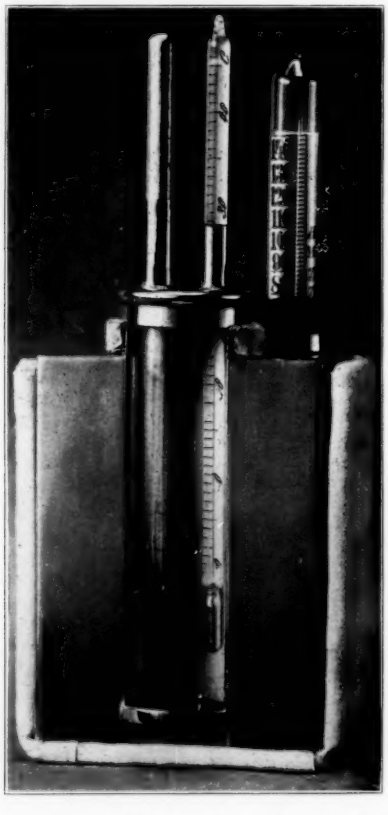
Tuberculosis, Class 2: 8 active cases—lungs, peritoneum, kidneys or general‡	8	10	11.7+	9-14+
Measles (eruptive stage) 10 positive, 3 "negative" results	12	13	9.5+	5-12
Varicella (eruptive stage)	4	4	11.8+	10-14
Croupous pneumonia (4 acute, 2 convalescing)	6	6	7.4+	5-10
Infantile atrophy	5	5	9.0+	6-12+
Rachitis	9	9	10.3+	6-12

‡One case showed no coagulation at the end of thirteen minutes.

It is clear that the number of cases in most of the classes examined is too small to permit of drawing conclusions. The figures, therefore, are presented merely to be of record.

From the results in a few diseases, however, it would be permissible to draw inferences.

Taking the average coagulation time of normal blood in childhood as 9.5 minutes (Biffi-Brooks method), we find that bronchopneumonia, which gives an average of 8.9 minutes uncomplicated, or 9.2 for all cases, seems



Biffi-Brooks coagulometer as modified by the authors. For description see text.

to exert no material influence on the coagulation time. According to Solis-Cohen, there is no uniformity in results with adults' blood in this disease, both a lengthened and shortened time having been found. In lobar pneumonia Rudolf and Cole found an average of 8.1 minutes in forty-seven observations on seventeen cases, Rudolf's average for normal children being 8.04 minutes.

Our figure of 7.4 + minutes for lobar pneumonia cannot be of much value for comparison, because it is based on so few observations.

Rudolf and Cole found an average coagulation time of 7.1 minutes (5-12 min.) in sixty observations on twenty-six cases of typhoid fever in children. This shows a greater reduction in coagulation time than we observed in our small number of cases (8.7 min., compared with 9.5 min. for normal cases).

In measles, the coagulation time was approximately normal (9.5 + min.). In tuberculosis, on the other hand, we found the most distinct change (Class 1, 11.5 min., Class 2, 11.7 + min.) of any — the difference between normal and diseased cases amounting to more than two minutes. If we were to take a positive von Pirquet reaction as a criterion for diagnosis of tuberculosis, this disparity might be increased, since several of the cases of rachitis which gave a lengthened coagulation time, would then have been included in the tuberculous class. We have, however, made the determination of tuberculosis depend on evidence of active, or very recently active, lesions.

Solis-Cohen and Vierordt found a shortened coagulation time in the blood of tuberculous adults, while Addis' results were the same as in normal cases. In no other class of disease did we find such uniform results as in tuberculosis, practically all of the cases showing a decided delay in coagulation.

The very short coagulation time in the one case of meningococcus meningitis (5 min.) and the lengthened time in nephritis with edema (15 min.) would be of greater interest were it not for the fact that these limits — five minutes and fifteen minutes — are not especially unusual for any class of cases. On the other hand, the one case in which we would expect to find a lengthened coagulation time (scurvy) gave a relatively short result (5.75 min.—two examinations).

Although the literature contains very little reference to the coagulation time in childhood as compared with adult life, the usual statement we find is to the effect that there is practically no difference except during the first few days of life, when a delay is observed.

Our results for older infants and children show no material differences from the accepted results, although the average for childhood is slightly higher than the average for adults tested by the Biffi method. (Authors, 9.5 min., Biffi, 7-10 min.)

Literature based on Biffi's original method or on the Brook's modification, contains nothing for comparison with children.

A study of our own and published results, according to various methods, emphasizes certain facts. *First,* that in each individual disease the maximum and minimum figures usually show a wide variation. We have alluded to this in referring to our figures for meningitis and nephritis. It is easy to see that the possibility of such variation in a selected case would be apt to negative the importance of the result. For example,

in our normal cases, we find a range of from five to fourteen minutes. Either figure by itself shows a far greater variation from normal than the *average* figure for any kind of disease in our classification.

In the same way Rudolf, using his own method,[1] found a variation of from five to twelve minutes in typhoid fever. (His limits in normal cases are not published.) Such variation, in spite of the utmost care and skill after long practice, seems to prove that the clinical method — at least that one not dependent on complicated apparatus — fails to indicate any but the most gross changes in coagulation time.

The *second* noteworthy fact is that the various diseases show *average* differences which can hardly be considered of any real importance, especially in view of the before-mentioned variation in the individual case. We would emphasize the importance of the fact that the *average* figures show much less variation than those for the *individual*.

Finally, we find rather more than the usual disagreement in the results of various observers. Allowing for the personal factor and the difference in technic and method, the inconsistencies still appear to be unduly conspicuous.

If these objections be true in regard to the results in adults, our work has proved them to be equally true in the case of the child, with the added disadvantage that the examinations of coagulability of blood in children are attended with increased difficulty.

It would seem to us that future efforts should be directed toward solving the problem of blood coagulation *per se*, or to a study of coagulability according to the more advanced standards, i. e., the determination of the presence or absence, increase or diminution, in one or more of the various elements concerned in the formation of thrombin and in the latter's action on fibrinogen.

It seems to us very improbable that any important variation exists in the mere time of coagulation of the blood in diseases other than of so-called hemorrhagic type. This opinion may be equalified by the statement that *average* differences of one, two or three minutes can hardly be construed as of any practical importance, especially when we consider the limitations and variations of the great majority of the so-called clinical methods. The chief value of the latter may be for comparison, yet, even in this case, the results must be interpreted with caution since the normal variation often is so great.

Of much more importance is the determination of the firmness and texture of the clot. For this reason it would seem that immersion in water is a more rigid test than that applied by most of the other clinical

1. Rudolf fills a capillary tube with blood and observes the formation of fibrin by breaking off sections of the tube at regular intervals.

methods and to this extent, at least, the method originated by Biffi presents distinct and practical advantages.

BIBLIOGRAPHY

Lidsky: Ztschr. f. klin. Med., 1910, lxxi, 343.
Schwarz and Ottenberg: Am. Jour. Med. Sc., 1910, cxl, 17.
Addis: Quart. Jour. Med., 1910-1911, iv, 14.
Howell, W. H.: Am. Jour. Physiol., 1910, xxvi, 453.
Howell, W. H.: Therapeutic Gazette, Feb. 15, 1912.
Solis-Cohen, Myer: Arch. Int. Med., 1911, viii, 684 and 820.
Whipple: Arch. Int. Med., 1912, ix, 365.
Addis: Quart. Jour. Exper. Physiol., 1908, i, 305.
Rudolf and Cole: Am. Jour. Med. Sc., 1911, cxlii, 481; 1910, cxl, 810.
Anders, J. M.: Tr. Am. Climatolog. Assn., 1907, xxiii, 127.
Kottmann: Ztschr. f. klin. Med., 1909-1910, lxix, 415.
Lucas: Boston Med. and Surg. Jour., 1909, clxi, 732.
Duke: Jour. Am. Med. Assn., 1910, lv, 1185.
Howell: Am. Jour. Physiol., 1911, xxix, 187.
Davis: Am. Jour. Physiol., 1911, xix, 160.

AN EARLY CASE OF CHONDRODYSTROPHY WITH RADIOGRAM AND NECROPSY*

L. E. LA FÉTRA, M.D.
NEW YORK

History.—The subject of this report, R. B., was admitted to the Infants' Ward of Bellevue Hospital, Nov. 1, 1911, five hours after birth. She was said to have been born at full term, and was delivered without difficulty by a midwife. As to the family history, there had been three other children, all of whom were dead, one at ten months and the other two, which were twins, at 2 months. No miscarriages nor stillbirths. There is no history of any similar deformities in the family and there are no dwarfs in the family connection; also no history of tuberculosis, syphilis nor any other constitutional disease.

Physical Examination.—Well nourished infant, the general appearance of the trunk resembling a seal. The skin is very cyanotic and the most striking feature about the face is the marked exophthalmos. The nose is short and saddle-shaped, with a deep depression at its root. The soft palate is fissured up to the posterior margin of the hard palate. The tongue is very large, filling up the entire posterior pharynx.

The heart sounds are normal; no murmur.

The liver is palpable at edge of costal margin; the spleen is not felt.

All the bones of the extremities are exceedingly short and their diameter is comparatively large; the flat surface of the long bones is wider than normal and the bones themselves are bowed, the normal curves being greatly exaggeration. The bowing is most marked at the epiphyseal ends of the bones.

The humerus is very short and the finger tips reach only to the crest of the ilium.

The left tibia is so short and so bent on itself that one's forefinger, if laid on the internal surface of the bone, is found to be simultaneously in contact with the upper tuberosity, with the shaft and with the internal malleolus.

Measurements: Head, circumference, 41.5 cm.; bitemporal diameter, 9 cm.; biparietal diameter, 11.3 cm., occipito-frontal, 12.7 cm.; occipito-bregmatic, 10.7 cm.; occipito-mental, 13.5 cm.; anterior fontanel, 6.3 cm.; posterior fontanel, 1.5 cm. long; bisacromial diameter, 12.7 cm.

Length: Crown of head to umbilicus, 25.2 cm.; umbilicus to sole of foot, 15.0 cm.; acromion-olecranon (arm-length), 6.3 cm.; diameter, 9.3 cm.; olecranon-wrist (forearm-length) 4.5 cm.; diameter, 8.3 cm.; hand, 5 cm. long; diameter, 7.5 cm.

---

*Specimen presented at the Annual Meeting of the American Pediatric Society, Hot Springs, Va., May 31, 1912.

Lower Extremity: Anterior superior spine to condyle, 7.5 cm.; circumference, 13.0 cm.; condyle to ankle, 7.5 cm.; circumference, 9.5 cm.; foot, 6.3 cm. long; diameter, 7.5 cm.

The thorax at nipple is 26.5 cm. in circumference; expansion is about 2 cm. December 19, the hemoglobin was 65 per cent.; red cells, 5,700,000; white cells, 17,400.

While in the hospital the baby was fed almost entirely on breast milk; but it gradually lost weight and died without symptoms of any definite disease at the age of 10 weeks. The weight on admission was 5 pounds, 4½ ounces; it had fallen to 4 pounds, 12 ounces before death.

Fig. 1.—Photograph taken at 1 week. It shows the exophthalmos, the pug nose, and the very short arm and forearm. The finger tips reach only to the crest of the ilium, and the fingers are not separated to form the "main en trident."

Radiographic examination of the whole body was made Nov. 9, 1911, by Dr. I. S. Hirsch, radiographer of Bellevue Hospital, whom I wish to thank for his skilfull work. His report is as follows:

RADIOGRAPHER'S REPORT

"The radiograph shows all the essential bony and joint changes characteristic of achondroplasia. There are no points of ossification for the epiphyses of

Fig. 2.—Photograph taken after death at 10 weeks. It shows also the marked thickening and bowing of the tibiæ.

any of the bones of the upper extremity; but the lower epiphyses of the femora are partially ossified. The diaphyseal portions of the bones are broadened and sharply outlined."

The *x*-ray print shows particularly well the shortening and thickening of the long bones. For comparison there is presented also the *x*-ray print of a normal though premature infant of practically the same length.

Fig. 3.—*X*-ray print of patient when 8 days old. It shows the characteristic shortening and thickening of the long bones.

PATHOLOGIST'S REPORT

Necropsy.—I wish to thank Dr. Charles Norris, the Pathologist of Bellevue Hospital, for his careful autopsy, for his interest and help in the study of the case, and for permission to make an abstract of the post-mortem record as follows:

Anatomic Diagnosis.—Chondrodystrophia congenitalis; rachitis.[1]

The body is that of a female child, 42 cm. long and weighing 2,270 gm. No description of the skeletal changes will be given because of the excellent *x*-ray photograph of the cadaver.

There is a very marked exophthalmus. Pupils normal. There are no external congenital anomalies. The vulvæ are large and swollen. The anterior fontanel is large, 5 cm. in width by 6 cm. anteroposteriorly. The posterior fontanelle is very small, but open. The sutures are wide. The face is of normal size. The right ear is thickened and red, showing a few superficial ulcerations on the antitragus. The left ear is normal.

There is a marked rosary, the swelling of the costochondral junctions being most marked internally. The ribs are long. There is a longitudinal groove just external to the costochondral junctions, but there is no Harrison's groove. The small intestines are markedly distended with gas. The peritoneal cavity contains blood-stained fluid (possibly due to post-mortem changes and freezing, the body having been frozen). The urachus is persistent, for a distance of about 1 inch. The cord is normal. There is a small umbilical vein. The sigmoid flexure is very long, extending well into the right side. The mucosa of the small and large intestines is everywhere very smooth, there being no solitary follicles or Peyer's patches visible.

Spleen: Weight 10 gm. It is 56 mm. by 25 mm. It is firm, dark red on section. No splenic follicles are visible.

Liver: Weight 90 gm., normal in size, dark red in color; serosa is everywhere normal and glistening; section dark red and smooth, without gross lesions.

Gall Bladder: This viscus is normal.

The mesenteric lymph nodes are everywhere small and somewhat yellowish in color.

Lungs.—The lungs show normal lobulations. The left lower lobe is completely atelectatic, red, firm, smooth on section, with extreme congestion. The posterior borders of all the lobes of the right lung are atelectatic. Otherwise the lungs and bronchi are normal.

Heart: There is no fluid in the pericardial cavity. The heart is possibly somewhat enlarged. The apex is formed by the left ventricle. There is a moderate *Rechtslage*, the aorta being visible and to the right of the pulmonary arteries. The right heart is somewhat large. There is a small foramen ovale. The ductus botalli is large. There is no stenosis of the isthmus. All the valves of the heart are normal. Musculature of the heart normal. The aorta and the vessels given off from the aorta are normal in distribution and appearance.

Pancreas: Weighs 5 gm.; is small; the lobulations are possibly not well developed. The head of the pancreas is somewhat red (post-mortem changes?).

Adrenals: The left adrenal weighs somewhat less than 2 gm., the right 1.25 gm. The left measures 32x25 mm., the right 15x13 mm. The cortex is very thin and pale. The medulla of both adrenals is hyperemic. There is almost no perirenal fat.

Kidney: The left kidney shows slight fetal lobulation. The pyramids are normal. Weight 13 grams.. The right kidney was not measured but appears to be of the same size and is similar in gross appearance.

The genital organs show no anomalies.

The thyroid gland is very small. The lobes are symmetrical. Both lobes weigh 1 gram. Thymus is small; weight 5½ grams. There appears to be almost no glandular tissue present. The fat of the anterior mediastinum is edematous. The tongue is about normal in size. Both tonsils are extremely small. The pharynx and larynx are normal. There is no hyperplasia of the lymphatic apparatus. The parathyroids were dissected out, seven being found.

---

1. For correction of this gross anatomical diagnosis, see note in microscopical examination.

Fig. 4.—*X*-ray print of healthy premature infant 14 days old, for comparison of long bones. The infant was 44 cm. long, or only 2 cm. longer than the chondrodystrophic infant.

Although there was no edema of the skin of the legs or arms, the subcutaneous tissues of the thorax and other portions of the body are everywhere slightly moist or edematous.

Head: Superficial examination of the brain, which was not opened until hardened, reveals no gross lesions. The dura appears everywhere to be slightly thickened. The foramen magnum is very narrow, showing marked irregularity; and the clivus is steep.

The foramen magnum is very peculiar, being distorted and irregular. The basilar portion of the ring is at a level 6 mm. below the occipital, and the shelving occipital portion is obliquely placed, so that the opening for the cord is oblique, its sagittal diameter running from the left anteriorly to the right posteriorly. This diameter measures 6 mm., while the longer obliquely transverse diameter measures 11 mm. The steep clivus is 28 mm. long.

On microscopic examination the thyroid gland shows an advanced grade of interstitial thyroiditis.

There is also an infiltration of small round-cells in the subcutaneous tissue and in the muscles, those from the abdominal wall alone being examined. Similar changes have been described in myxedema.

As to the gross anatomic diagnosis of rachitis, it should be recorded that the sections taken from the costochondral junctions and from the femur show no evidence of rachitis, the lesion being characteristic of chondrodystrophy with an extreme grade of mucous degeneration of the cartilage cells.

The case reported, while exhibiting the characteristic features of chondrodystrophy, must be regarded, in view of the gross and microscopic examination, as one of mixed type. There is no redundancy of skin on the lower extremities, there is no trident hand; there is a congenital anomaly in the cleft palate, and there is evidence of thyroid deficiency which has probably no etiological significance. The general subject of chondrodystrophy has been so thoroughly discussed in recent literature that here no description of the disease will be attempted. For a full consideration of the subject the reader is referred to Kaufmann's monograph on "Chondystrophia Fœtalis," and to the admirable volume on "Dwarfism" in the Eugenics Laboratory Memoirs XV, Section XV, a. Here will be found a complete discussion of achondroplasia by Dr. H. Rischbieth, together with a résumé by Amy Barrington of the Bibliography of Dwarfism, and reproductions or descriptions of the dwarfs (mostly chondrodystrophic) depicted by famous painters.

113 East Sixty-First Street.

METHODS OF ESTIMATING KIDNEY FUNCTION*

RICHARD M. SMITH, M.D.
BOSTON

Various methods have been employed in the estimation of kidney function. These methods may be divided roughly into (1) a study of the excretion of normal constituents of the urine, principally water, sodium chlorid and urea; (2) the determination of the freezing point of urine as compared with body fluids; (3) a study of the excretion of certain substances not normally found in the urine, introduced into the body for the specific purpose of the investigation of their elimination by the kidney. These substances include iodin, methylene-blue, phloridzin, indigo-carmin and numerous other drugs. One might also mention in this connection a further method of study by ligature of the vessels of the kidney. Investigations have been conducted on kidneys whose action was supposed to be normal and on kidneys known to be pathologic. The chief interest has centered in the pathologic conditions, for it is with the diseased kidney that physicians have mostly to deal. Furthermore, in a pathologic kidney it becomes of supreme interest to determine how greatly the kidney is damaged and how much the departure from normal which exists influences the ability of the kidney to perform its function and whether the remaining function is sufficient to sustain the life of the individual. A further interest is aroused as to whether the functional capacity of the kidney bears any direct relation to its anatomic condition and whether that relationship is a constant and a proportional one. It is my intention to discuss the various methods of estimating kidney function and the results obtained from them only in the barest detail, and to devote the greater part of my time to the consideration of the most recent method of determining the functional capacity of the kidney.

The elimination of water by the kidneys takes place largely through the glomeruli.[1] This matter seems fairly well determined by numerous investigations on both animals and man. Whether this process is due to any action of the glomeruli themselves or whether these structures act simply as a filter has not yet been absolutely determined. The consensus of opinion seems to be that water is eliminated by filtration and that the cells of the glomeruli enter to a slight degree only, if at all, into the process.[2] It is possible that water elimination may be dependent on the

*From the Children's Medical Department, Massachusetts General Hospital.

*Read in the Section on Diseases of Children of the American Medical Association, at its Sixty-Third Annual Session, held at Atlantic City, June, 1912.

1. Karsner, H. T.: Jour. Am. Med. Assn., 1911, lvi, 1452.
2. Frey, E.: Deutsch. Med. Wchnschr., 1911, xxxvii, 1072.

elimination of sodium chlorid. It is certainly true that sodium chlorid and water elimination are closely associated with one another[3] and this relationship is so close that a study of water elimination alone cannot be an accurate basis for the estimation of the function of the kidney. It has been shown that there may be great variations in the water elimination in perfectly normal kidneys and that in damaged kidneys there may be either polyuria or oliguria or normal water elimination.[4] General circulatory disturbances or injury to the vessels of the kidney which must influence the passage of blood through the glomeruli will affect the secretion of water. The ability of the kidney to eliminate water is really no test of the functional capacity of the organ.

Sodium chlorid excretion takes place through the glomeruli. Certain investigators, however, say that conclusions based on the supposition that sodium chlorid is eliminated in certain portions of the kidney are not worthy of consideration.[5] The process of elimination is largely one of filtration and not of active secretion on the part of the cells of the glomeruli. The metabolism of sodium chlorid is closely associated with the condition of edema.[6] Presumably sodium chlorid acts as a cause and not as an effect, but in any event a complication to the study of salt excretion is presented. A further difficulty arises from the effect of other salts on sodium chlorid excretion.[7] Any conclusions as to the functional capacity of the kidney drawn from sodium chlorid determinations are open to possibilities of grave error.

The estimation of urea elimination is of special interest because nitrogen metabolism is supposed to be associated with certain toxemias, as uremia, but the relationship is not invariable. Probably the largest amount of investigation has been done on this phase of body metabolism in its relation to the function of the kidney.[8] It is generally agreed that urea is eliminated through direct action of the cells of the kidney tubules and is therefore a true secretion.[1] The methods of estimating urea elimination are difficult and the subject is so complicated by the question of diet and other considerations that for practical clinical purposes this method of estimating the function of the kidney is hardly feasible.

When we consider the estimation of kidney function through the introduction into the body of a substance not normally found in the urine

---

3. d'Amato, L.: and Faggella, V.: Ztschr. f. klin. Med., 1911, lxxii, Nos. 5 and 6, 474.

4. Schlayer: Deutsch. Arch. f. klin. Med., 1911, cii, 311.

5. Hoessein and Kashiwade: Deutsch. Arch. f. klin. Med., 1911, cii, Nos. 5 and 6, 520.

6. Vogel, K. M.: Deutsch. Arch. f. klin. Med., 1911, vii, 602.

7. Lavenson, R. S.: Abstr. Jour. Am. Med. Assn., 1911, lvii, 150.

8. Ambard and Moreno: Semaine méd., 1911, xxxi, 181; Widal: Jour. méd. Francais; Rev. in Le Monde Med., 1912, xxi, 265; Wells, E. F.: Jour. Am. Med. Assn., 1911, lvii, 1184.

we pass into an entirely different field of study. I shall say nothing of the various dyes and drugs used in this investigation, except with reference to the one most recently employed, namely, phenolsulphonephthalein. The use of this drug was first introduced into medicine by Geraghty and Rowntree,[9] of Baltimore, and has now had a fairly wide application all over this country.[10] It has been employed chiefly in surgical conditions, but a considerable amount of data has been accumulated on its use in cases of acute and chronic nephritis. My interest in this test was first aroused in 1909 in connection with work on experimental nephritis in rabbits.[11] Since that time I have used the test both in animals and in human beings.

It will be unnecessary to go into a detailed description of the technic of this test, for most of you are already familiar with it. Suffice it to say, that it consists of the injection into the body of a small amount of the drug, and the determination of the time at which it appears in the urine and the proportionate amount eliminated by the kidney in a given space of time. Six mg. in a 1 c.c. solution is the dose usually employed. I have used one-half this amount in the work with infants and children. This drug is particularly useful for this method of investigation because it is practically all eliminated by the kidney without change in the body, because its elimination occurs in a very short time and because it causes no disturbance to the individual. The drug is a brilliant red color in alkaline solutions and the variation in the depth of this color is directly proportionate to the amount of drug present in the solution.

The injection may be given either subcutaneously, intramuscularly or intravenously. In the intravenous method the elimination of the drug by the kidneys is so rapid that the normal variations of kidney function over so short a period of time makes this method less accurate than the others. By the subcutaneous and intramuscular methods the question of the absorption of the drug enters into the results. But with intramuscular injection the variation in absorption as proved by numerous experiments is so slight that it may be disregarded.[12] Therefore, this is the method of choice. For the sake of uniformity, all the cases here reported were given subcutaneous injections, since this method was used in the first tests.

After the drug has been injected, the patient is catheterized and the urine received into a strongly alkaline solution. When the first pink color appears the time is noted. In adults with normal kidneys this time is about ten minutes. I have found this to be true also in normal rabbits[11] and in normal infants and children.

---

9. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1909-10, i, 579.

10. Geraghty and Rowntree: Jour. Am. Med. Assn., 1911, lvii, 811; Boyd: Jour. Am. Med. Assn., 1912, lviii, 620; Keyes, E. L., Jr.: Am. Jour. Uro., 1911, vii, 125.

11. Smith, R. M.: Arch. Int. Med., 1911, viii, 508.

12. Rowntree and Geraghty: Arch. Int. Med., 1912, ix, 284.

TABLE 1.—CASES WITH NORMAL KIDNEYS UNDER PHENOLSULPHONEPHTHALEIN TEST

Case No. ...	Diagnosis	Time Appeared After Injection, Minutes	Per Cent. Excreted In One Hour
1.	Hodgkin's Disease	10	46
2.	Feeding	8	50
3.	Feeding	23	32
4.	Abscess of lung	11	52
5.	Chorea (convalescent)	9	47

All the urine that is passed during the hour following the appearance of color is collected. In female infants it is necessary to leave the catheter in the bladder during this time. In male infants a test-tube may be attached securely to the penis and the urine collected in this, and the patient catheterized at the end of an hour. Older children can void when the hour has passed and only the first catheterization is necessary. This urine is diluted to a certain given amount, usually 1,000 c.c., and is made strongly alkaline. The color of the diluted urine is compared with the color of a solution containing a known amount of the drug in the same amount of liquid. As first suggested, this comparison necessitated the employment of a colorimeter, but Cabot and Young[13] introduced the use of a series of test-tubes containing varying percentages of the drug. This method I have found perfectly satisfactory and very simple and inexpensive. There is some difficulty in making the comparison in certain instances owing to the coloring matter present in the urine. This difficulty can be eliminated by the simple device suggested by Whitney, of looking at the fluids through a yellow glass.[14] The normal kidney eliminates during the first hour from 40 to 60 per cent. of the drug injected.

Rowntree and Geraghty[12] have shown by experiments on frogs that the elimination of phenolsulphonephthalein is a definite secretion of the kidney tubules. This is further borne out by the fact that after injection none of the drug is found in the pancreatic juice or the saliva, and only the very slightest trace in the bile. Experimentally, the drugs which stimulate the renal cells to action, such as caffein, produce an increased secretion of phenolsulphonephthalein, while those drugs which act only through the circulation, as digitalis, have no effect. Clamping of the renal artery which produces a severe anemia of the kidney and an obstruction of the function of the tubules, causes a deficient secretion of phenolsulphonephthalein.[15] Clinically, cases of marked anemia producing the same effect show a small secretion of the drug.

In a previous paper[11] I have reported the use of this test in animals with experimental nephritis. In these animals the lesions were produced

13. Cabot and Young: Boston Med. and Surg. Jour., 1911, clxv, 549.
14. Whitney, J. L.: Jour. Am. Med. Assn., 1912, lvii, 936.
15. Eisenbrey, A. B.: Jour. Exper. Med., 1911, xiv, 462.

by uranium nitrate and potassium bichromate which cause lesions in the tubules, and by arsenic which causes no anatomic lesions, but does cause a decrease in the function of the glomeruli. In both groups of animals there was a considerable proportion of cases with delayed secretion. In later experiments Eisenbrey[15] found delayed secretions in animals which had received uranium nitrate and arsenic, and also in animals which had received cantharidin, which causes actual lesions of the glomeruli. So it is evident that the glomeruli enter in some measure into the elimination of phenolsulphonephthalein even though the tubules are primarily concerned.

It has been impossible to establish any definite relationship between the excretion of phenolsulphonephthalein and the elimination of water, sodium chlorid and nitrogen.[12, 16]

The following cases will illustrate this point:

CASE 6.—Acute nephritis. Protein in diet, 35 gm.; in urine, 36 gm. Chlorids in diet, 1.5 gm.; in urine, 1.25 gm. Phen. test: Color appeared in fifteen minutes; 50 per cent. excreted in one hour. One month later the interval was reduced to eight minutes and 45 per cent. was excreted in one hour.

CASE 7.—Acute nephritis. Protein in diet, 32 gm.; in urine, 24.8 gm.; chlorids in diet, 1.5 gm.; in urine, 1.25 gm. Phen. test: Color appeared in fifteen minutes; 30 per cent. excreted in one hour. One month later, time interval eleven minutes; 40 per cent. excreted in one hour.

CASE 8.—Acute nephritis. Protein in diet, 56 gm.; in urine 22.37 gm. Test: Time interval, fifteen minutes; 30 per cent. excreted in one hour. Three weeks later protein in diet, 65.87 gm.; in urine, 27.17 gm. Test: Time interval nine minutes; 40 per cent. excreted in one hour.

Animals given repeated doses of kidney irritants will show a decrease in phenolsulphonephthalein secretion with the onset of vomiting and signs of toxemia, even before there is any change in the elimination of nitrogen or chlorids. Therefore, we should expect that deficient elimination of phenolsulphonephthalein would be closely associated with uremia. A number of cases reported by various investigators show this to be a fact. It is possible in patients manifesting no clinical symptoms of nephritis or of impending uremia to predict imminent danger when the phenolsulphonephthalein elimination is extremely low. It is doubtful if any patient having a complete retention of the drug or a very slight excretion can survive many weeks.

Patients with acute nephritis show, as a rule, normal or only slightly diminished secretion.

Ten patients with acute nephritis were given the test at various stages in the disease. The time of appearance of the color in the urine varied from eight to twenty minutes, and the per cent. excreted in one hour, from 28 to 61. There was no constant association between the long time appearance and the small per cent. of excretion, nor between either one

16. Austen, F. H., and Eisenbrey, A. B.: Jour. Exper. Med., 1911, xiv, 366.

of these and the severity of the clinical condition of the patient. Four of the six cases on which the test was repeated when the patient had improved showed a reduction in the time appearance of the drug. One showed a longer time and one was the same, fourteen minutes, after an interval of seven weeks, during which time the urine had become entirely normal. In these same six patients the per cent. of drugs excreted in the retest was more than in the first test, in four cases, the same in one and less in one. The patient who showed a decrease in the amount excreted was the one who showed the greatest reduction in the time interval.

TABLE 2.—TEN CASES OF ACUTE NEPHRITIS SUBJECTED TO SULPHONEPHTHALEIN TEST

Case No.	Date	Time of Appearance Minutes	Per cent. in One Hour	Urine	Remarks
6	12/11/11	20	50	Alb. +; blood ++; casts +	B. P. 120 sl. edema
	1/10/12	8	45	Alb. s. p. t.; blood little; casts few	B. P. 105 sl. edema
7	12/11/11	15	30	Alb. ++; blood +; casts ++	B. P. 190 sl. face
	1/10/12	11	40	Alb. v. s. t.; blood little; casts many	B. P. 100 no edema
8	2/16/12	15	35	Alb. sp. +; blood +; casts +	B. P. 100 no edema
	3/ 2/12	9	40	Alb. v. s. t.; blood 0; casts rare	
9	1/11/11	15	61	Alb. 1 per cent. +; blood +; casts +	Sl. edema
10	3/ 8/11	14	49	Alb. +; blood +; casts +	No edema
	5/28/12	14	55.5	Normal	
11	5/28/11	13	48	Alb. +; blood ++; casts +	Sl. edema
	6/ 3/12	9	52	Alb. +; blood ++; casts +	Sl. edema
12	9/16/11	8	30	Alb. ++; blood +; casts +	Mod. edema
	9/25/12	10	30	Alb. 0; blood 0; casts 0	Later urine showed little alb. No casts.
13	10/12/11	15	28	Alb. ++; blood ++; casts ++	Sl. edema. Acute endocarditis. B. P. 120
14	6/20/11	9	30	Alb. +++; blood +; casts +	B. P. 120. Sl. edema
15	3/11/12	16	34	Alb. ?; blood 0; casts +	B. P. 118. No edema

CASE 6 (cited also above).—Aged 6 years. Acute nephritis apparently following a nasal pharyngeal infection. Urine contained a large amount of albumin, blood and many casts. No edema. Blood-pressure 120, which later came down to 105. Protein in diet, 35 gm.; in the urine, 36 gm.; chlorids in the diet, 2.5 gm.; in the urine .75 gm. Test: Time of appearance of the dye twenty minutes and 50 per cent. excreted in first hour. Test repeated one month later when the urine had considerably improved but still showed nephritic elements; time eight minutes, 45 per cent. excreted in the first hour.

CASE 7 (cited also above).—Aged 4 years. Acute nephritis, apparently following tonsillitis. At the time of entrance the urine showed a large amount of

albumin, much blood, and casts. Blood-pressure 150 to 190, which later fell under improvement to 90. Slight edema of the face. Proteins in the diet 32 gm.; in the urine, 24.8 gm.; chlorids in the diet, 1.5 gm.; in the urine 1.25 gm. Test showed time of appearance fifteen minutes; 30 per cent. excreted in first hour. Test made one month later showed marked improvement in condition of patient; time eleven minutes, excretion 40 per cent.

CASE 8 (cited also above).—Aged 9 years. Acute nephritis. About one month's duration. Blood-pressure 100. Urine showed slightest possible trace of albumin, a little blood and a moderate number of casts. Protein in diet, 56 gm.; excreted, 22.37 gm. Test, color appeared fifteen minutes after injection; 35 per cent. excreted in the urine first hour. Second test three weeks later; protein in the diet, 65.87 gm.; in the urine 27.17 gm. Time of appearance of drug, nine minutes; 40 per cent. excreted in first hour.

TABLE 3.—RESULTS OF SULPHONEPHTHALEIN TEST IN FIVE CASES OF PYELITIS (COLON)

Case No.	Time of Appearance Minutes	Per cent. in One Hour
16	10	30
17	11	60
18	21 (—)	35
19	10	20
20	14	55
21	7	22

CASE 9.—Aged 3½ years. Acute nephritis. Duration of the disease not known. Possibly chronic nephritis. Urine shows large amount of albumin, a little blood, many casts. Slight edema. Time of appearance, fifteen minutes; excretion of drug 61 per cent. in the first hour.

CASE 10.—Aged 7 years. Acute nephritis following influenza. Urine showed a large amount of albumin, considerable blood and casts. No edema. Test color appeared in fourteen minutes; 45 per cent. excreted in first hour. Fourteen months later test repeated. Urine normal. Time of appearance of drug, fourteen minutes; 55.5 per cent. excreted in first hour.

CASE 11.—Aged 5 years. Acute nephritis. Urine showed small amount of albumin, much blood and moderate number of casts; slight edema. Test showed time of appearance thirteen minutes; 48 per cent. excreted in first hour. Repeated five days later. Time of appearance nine minutes; 52 per cent. excreted in the first hour.

CASE 12.—Aged 3½ years. Acute nephritis. Possibly chronic nephritis. Urine showed albumin, blood and casts. Moderate edema. Time of appearance of the drug eight minutes; 38 per cent. excreted in the first hour. Repeated nine days later when the urine had become practically normal. Time interval, ten minutes; amount of excretion 30 per cent.

CASE 13.—Aged 6 years. Acute nephritis. After tonsillitis. Urine showed a large amount of albumin, much blood and many casts. Slight edema. Blood-pressure 120. Test showed time of appearance fifteen minutes; 28 per cent. excreted in first hour. Four months later the urine was entirely normal.

CASE 14.—Aged 7 years. Acute nephritis following tonsillitis. Urine showed a large amount of albumin, blood and casts. Moderate edema. Blood-pressure 120. Test, time of appearance nine minutes; 30 per cent. excreted in first hour.

CASE 15.—Acute nephritis. Urine showed only a rare cast. No edema. Test, time sixteen minutes; amount excreted 34 per cent.

I have used the test in six cases of pyelitis and give the results, though of course, the number is too small from which to draw conclusions. The time of the appearance of the drug varied from seven to twenty-one minutes, and the amount excreted in one hour from 20 to 60 per cent.

It is possible by the use of this test in cases which present evidence of both renal and cardiac disease to determine which factor is primarily at fault. There may be a temporary decrease in the phenolsulphonephthalein excretion due to edema and passive congestion, but this decrease is relatively small in amount and transient in character as compared with the cases in which the primary lesion is in the kidney and the cardiac complication is secondary.

CASE 22.—A child of 20 months under observation in the hospital has marked cardiac disease with general edema. The urine is normal except for the slightest possible trace of albumin. The blood is normal, hemoglobin 85 per cent. The phenolsulphonephthalein secretion at entrance was 15 per cent. and the drug appeared in the urine in twenty minutes after injection. One week later, when the general condition had markedly improved the time interval was sixteen minutes and 23 per cent. was excreted in the first hour, showing an improving functional condition of the kidneys.

I was unable, in animals with experimental nephritis, to show a constant relationship between the findings of the test and the anatomic condition of the kidney. Later investigations have agreed with this[15] and would seem to indicate that the reduction in the excretion of the drug is roughly proportionate to the dose of the poison.[12]

In man, all cases showing very marked delay in secretion, however, have showed distinct lesions of the kidney at autopsy.

This test gives information which may be of aid in the care of patients with nephritis. It shows the ability of the kidney to eliminate toxins and whether there is danger of uremia. It does not assist in determining the ability of the kidney to eliminate proteins, salt and water. There have been some exceptions to the general principles which I have tried to outline in relation to the use of this test, but it seems to me that the results obtained have been sufficiently consistent and valuable to warrant its much wider application in medical practice.

329 Beacon Street.

BIBLIOGRAPHY

The following references are included but not specifically cited:
Nobecourt: Méd. inf. Par., 1911, viii, 121.
Monakow: Deutsch. Arch. f. klin. Med., 1911, cii, Nos. 3 and 4, 248.
Blum, V.: Wien. klin. Wchnschr., 1911, xxiii, No. 19, 685.
Heitz, Boyer and Moreno: Presse méd., 1911, xix, 245.
Katz and Lichtenstern: Wien. klin. Wchnschr., 1911, xxiv, 811.
Thomas, B. A.: Surg. Gyn. and Obst., 1911, xii, 345.
Marinacci, G.: Policlinico, 1911, xviii, 145.
Roth: Ztschr. f. Urol., 1911, v, 439.

THE VACCINE THERAPY OF WHOOPING-COUGH

ARRIE BAMBERGER, M.D.
Assistant Professor of Clinical Pediatrics, College of Physicians and Surgeons
CHICAGO

Because of the unpleasant and distressing symptoms of whooping-cough, a large number of drugs, as well as other supposed remedial agents, have been tried in its treatment, all of which have met with more or less failure. Since the discovery of the supposed specific bacillus of whooping-cough by Bordet and Gengou in 1906, the trend has been to develop a specific vaccine or serum.

The bacillus of Bordet and Gengou grows deeply in the remoter parts of the respiratory tract, seldom above the level of the larynx and oftener below it, and is found in largest numbers during the early stage of the disease. It is a small, ovoid bacillus, non-motile, gram-negative, stains feebly with the ordinary basic dyes, and grows best on a mixture of defibrinated human or rabbit's blood with 3 per cent. agar.

In 1909, Lehman,[1] a homeopath, reported successful treatment of whooping-cough with coqueluchin, which he describes as made from the virus of the disease, triturated, and then given either hypodermically or by mouth. Graham,[2] a few months ago, after using the vaccine of the Bordet and Gengou bacillus, reported the following results: From a series of twenty-four cases, seventeen were apparently benefited and seven apparently not benefited. He first used the dose of 20,000,000 bacteria every four days, then 40,000,000 every four days, then every three days, and finally every second day without any untoward effects; none receiving less than six injections of 40,000,000 each, and none more than eight.

The vaccine I used was prepared from deep swabbings of the throat of children having pertussis, each cubic centimeter containing 20,000,000 dead organisms. The cultures are plated and replated until a pure culture is obtained; the vaccine is then made from several strains of the bacilli, so that it is polyvalent in character.

I can report only six cases under this treatment, but am taking the privilege of reporting this small number because the treatment is still in the experimental stage, and the more we hear about it the better we can draw conclusions as to its value. All of my cases were clinic patients of the poorer class of society, who are less apt to react to this treatment than children of the better class. I used a dosage of 20,000,000 bacteria every other day; no case receiving less than five injections, and none more than

1. Clinique, Chicago, 1909, xxx, 659.
2. Am. Jour. Dis. Child., January, 1912.

fifteen. A daily record of the temperature, pulse and number of paroxysms was kept in all cases, so that we obtained a fairly accurate idea of the effect of the vaccine. The vaccine was injected hypodermically in the gluteal region, the part first washed with soap and water, and then with alcohol. There were no constitutional effects such as fever, rashes, rheumatoid pains, vomiting or malaise during the treatment, and a local reaction, as a few small blisters at the site of injection, occurred just once in one case. The children ranged in age from 1 to 4 years. The results of the treatment were as follows:

Case	Number of Injections	Duration After Treatment, Days	Total Duration Days
1	5	13	30
2	9	18	42
3	7	16	30
4	8	18	28
5	15	30	41
6	8	22	32

CASE REPORTS

CASE 1.—J. C., male, aged 3, began treatment during third week of disease; was having seven paroxysms in twenty-four hours. First injection 4/23/12, in usual way. On 4/29/12, after 3 injections, the paroxysms were four in twenty-four hours and very mild, and on 5/9/12, after five injections there were no paroxysms and the child was in good general condition. Total duration of disease thirty days, duration after treatment began, thirteen days.

CASE 2.—L. S., female, 4 years old, began treatment during the fourth week of the disease. First injection given 5/9/12, when she was having five paroxysms a day. On 5/15/12 after three injections there were no paroxysms at night, and on 5/25/12, after eight injections there was only one paroxysm, and on 5/27/12, after nine injections no paroxysms, and the child was in good general condition. Total duration of the disease forty-two days; duration after treatment began, eighteen days.

CASE 3.—L. S., male, 2½ years old, began treatment during second week of disease. First injection 5/9/12, when he was having four paroxysms a day. No change in condition until six injections were given, when there were only two paroxysms in twenty-four hours. On 5/25/12, after the seventh injection there were no paroxysms and the child was in good general condition. The total duration of the disease was thirty days; duration after treatment began was sixteen days.

CASE 4.—C. F., female, 1 year old; first seen at beginning of second week. Injection began on 5/11/12, when the paroxysms were very severe and so frequent that the mother could not keep count of them. On 5/17/12, after three injections, the paroxysms were less frequent and less severe On 5/22/12, after five injections, there were three paroxysms in twenty-four hours; on 5/24/12, one paroxysm and on 5/29/12, after eight injections, no paroxysms and the child was in good condition. Total duration of disease, twenty-eight days; duration after treatment began, eighteen days.

CASE 5.—F. B., female, 2½ years old; seen first during second week of disease. Injections began 5/10/12, when there were eighteen paroxysms in twenty-four hours. After seven injections, on 5/27/12 there were eight paroxysms a day; on 6/10/12, after fifteen injections there were no paroxysms, but a slight cough persisted. This case was not markedly shortened or benefited by the treatment, except that no complications followed which was gratifying in view of the young

age of the child. Total duration of disease, forty-one days; duration after treatment began, thirty days.

CASE 6.—L. B., female, 1 year old; began treatment during second week of disease. First injection was given on 3/22/12, when there were ten paroxysms a day. After five injections on 4/5/12, there were four paroxysms. After eight injections on 4/10/12 there were no paroxysms and child was in good general condition. Total duration of disease was thirty-two days; duration after treatment began, twenty-two days.

CONCLUSIONS

1. The treatment seems rather to lessen the severity of the disease and abort complications, than to shorten the duration markedly, although only two of my cases lasted as long as six weeks.

2. The sooner the treatment is begun, the better the results.

3. I used less vaccine than Graham; his minimum dose was 240,000,000 and maximum 320,000,000, while my minimum was 100,000,000 and maximum 300,000,000. Nevertheless, I should advise larger doses, say 500,000,000, and more frequent, as every day, as I think the course of the disease can be cut short by so doing.

4. I believe this method of treating whooping-cough is deserving of a trial, as it certainly is harmless and may prove to be of great value.

I desire to express thanks to Parke, Davis & Co. for supplying the vaccine gratis; and also to Miss Winn of the Visiting Nurse's Association, for her kind cooperation in this work.

32 North State Street.

FAT AND NITROGEN METABOLISM IN A CASE OF CONGENITAL ABSENCE OF THE BILE-DUCTS WITH A STUDY OF FERMENTS OF THE PANCREATIC SECRETION AND THE FECES

HENRY KOPLIK, M.D., AND BURRILL B. CROHN, M.D.
NEW YORK

In this study of fat metabolism, with a consideration of the nitrogen balance in a case of congenital absence of the bile-ducts, we were especially concerned from a clinical standpoint, not only with the fat and nitrogen disposition in the body, but with the activity of the pancreatic ferments. In this, one of us (Koplik) was fortunate in having the active co-operation of a colleague skilled in studies of such a nature.

From a clinical standpoint it is of importance to ascertain whether the ducts are stenosed or absent, or practically occluded. There are cases of stenosis of the bile-ducts in which considerable bile passes into the intestine; such a case we have seen lately. In this case also there was the anomaly of a very large colon (Hirschsprung). In such a case metabolism studies would be of uncertain value on account of the abnormal state of the large, or even the small, intestine.

In the case which forms the subject of this present study the abnormal condition, as far as could be defined clinically, was that of a pure absence of the bile-ducts without any anomaly of the stomach or intestine being evident. Such cases are not numerous in the literature. The finding of a definite pancreatic secretion, with the study of its fermentative powers, is of great interest, occurring, as it does, in so young an infant.

METABOLISM BED

A word of explanation may not be out of place as to the metabolism bed. This bed was devised by one of us (Koplik) to confine the movements of the infant as little as possible. Of course all ideas of any metabolism bed must be traced back to the original bed of Heubner. From this all the others must derive their construction. The bed used in this case is an inclined Bradford frame devised in such a way as to maintain the pelvis of the baby in a fixed position. The frame itself is suspended from the head and foot of the bed like a hammock. The arms and lower extremities are absolutely free, the abdomen is not pressed on, the baby is safe and happy and does not seem to be the least incommoded. To prevent the baby from falling off the frame the chest is dressed in a loose corset-waist with bands at the sides so that the baby cannot fall to one or the other side, but at the same time has some latitude of motion. The baby also is not chilled, for by means of radiation from warm water bags beneath the frame an equable temperature is maintained. The exposed buttock and other parts are not chilled. The babies may actually gain in weight, at least do not lose, and seem perfectly happy. We have used this bed quite often and are well pleased,

inasmuch as we feel that the ultimate results are vitiated as little as possible by the enforced rest.

CASE REPORT

M. E., aged 10 weeks, was studied from Jan. 5 to Feb. 4, 1912. The diagnosis was congenital absence of the bile ducts.

Family History.—Negative for tuberculosis. The mother was married two years; this was the first child; no miscarriages.

Past History.—Breast-fed since birth; feedings q. 2 h. 15 to 30 minutes. Mother had little milk. Labor not especially difficult. Child was in a hospital for two weeks.

Present History.—The mother first noticed that the child was jaundiced when she was a week old. She did not know whether the child was yellow during the first week. Since the first week the child's stools were whitish. For over seven weeks the urine was dark. The child was becoming more jaundiced. The mother had noticed spots on the back only during the previous week.

Physical Examination.—General condition good; well nourished.

Skin: Intense greenish jaundice of skin and of mucous membranes. On back about middle of lumbar region there were three large, separate hematomata, the areas being infiltrated and just under the skin. Just under the free border of ribs on left side below axilla, another hematoma. Hematoma on right arm and right buttock.

Eyes: Icterus of conjunctiva, otherwise negative.

Mouth: Tongue clean, frenum short, prevents active movement of tongue.

Pharynx, ears and mastoids, glands, spine, chest, lungs and heart were negative.

Liver: Edge felt about four fingers (9 cm.) below free costal border in mammary line; moderately firm; gall-bladder not palpable.

Spleen: Edge felt one finger below free border.

Abdomen: Negative except for small umbilical hernia.

Extremities: Hematomata as noted. No Kernig or Babinski.

January 8.—Stool: Silvery white, of pasty consistency. The child was placed on the metabolism bed January 8.

January 9: Coagulation time of blood 5½ minutes. W. B. C., 7,600; Polynuclears, 48 per cent.; S. L., 44 per cent.; L. L., 8 per cent.; Hgb., 55 per cent. Blood contained bile. Urine normal except for heavy bile staining.

January 13: General condition fair; jaundice seemed somewhat more intense. Child for four days was on metabolism bed with apparently no discomfort. Stools clay colored. Urine contained considerable bile; weight practically at a standstill.

January 17, 9 a. m.: Soft rubber catheter No. 15 French passed gently into stomach, and slowly pushed to length of 25 cm. from the gum line. Felt apparently to enter duodenum. Aspirated with negative pressure for one hour. About 10 c.c. clear mucoid fluid obtained, very mucoid and stringy, neutral in reaction. The child was quiet throughout, though apparently hungry.

January 18: General condition fair; jaundice at a standstill; greenish yellow. Temperature normal. Weight seemed about stationary. The ecchymotic spots had practically disappeared.

January 26: Condition fair; temperature normal; jaundice seemed, if anything, somewhat lighter. Only remnants of ecchymoses were present on body; no new ecchymoses anywhere. General physical condition otherwise unchanged. Liver in mid-clavicular line was 7.5 cm. below free border; gaining in weight.

February 4: Condition about the same. Jaundice seemed stationary; temperature normal; stationary in weight. No new ecchymoses. Heart and lungs normal. Liver edge felt 6 cm. below free border in mid-clavicular line. Spleen felt at free border of ribs. Stools still show no evidence of bile.

February 6: Discharged with weight 8 pounds 5 ounces, but in very good condition.

February 9: It was learned that soon after leaving the hospital the child began to fail rapidly. Death took place three days later. No autopsy was obtainable.

TABLE OF WEIGHT OF THE BABY

	Pounds	Ounces
January 6, after admission	8	11
January 8, put in metabolism bed, 10 a. m.	8	11½
January 11, just before removal from bed, 12 m.	8	11
January 12, 6 p. m., taken out of metabolism bed.		
January 14	8	8
January 18	8	9
January 22	8	8
January 25	8	10
January 29	8	8
February 1	8	6
February 3	8	5

Temperature and pulse normal throughout the period of observation.

LABORATORY FINDINGS

1. Methods: The following chemical and metabolism studies were effected by placing the child in a metabolism frame for a period of four days. During this time the intake of the child was most carefully noted, an exact duplicate diet being reserved for chemical analysis. The excreta were collected, urine and stool separately, as far as possible (stool being strained off through a sieve), the whole being iced immediately and so maintained for analysis. The twenty-four-hour specimen of urine was daily examined chemically and for ferments. The daily stool was similarly analyzed for the presence of ferments; the chemical data on the stool was ascertained from the accumulated total period collection.

Nitrogen estimations were made by the Kjeldahl process; total fat analysis of the stool with estimations of the split fat, by means of the Folin-Wentworth method.

The total solids of the milk was reckoned by drying and difference; fat reckoned by extraction of the dried residue with warm ether. The methods of ferment analyses will be described later.

2. Metabolism Studies: A computation of the intake of the child during the four-day period is represented in Table 1.

TABLE 1.—ANALYSIS OF FOOD INTAKE IN AUTHOR'S CASE

Date	Milk Amount, c.c.	Total Solids, Per Cent.	Total N, Gm.	Fat, Gm.	Remarks
January 9	900	5.52	2.091	13.95	Diet, Jan. 9-10: Whole milk, ℥viii; barley gruel, ℥xvii; milk-sugar ℥v.
January 10	825	5.2	1.478	10.31	
January 11	1,110	6.8	1.771	23.20	Diet, Jan. 11-12: Whole milk, ℥xv; barley gruel, ℥xx; milk sugar ℥ vi.
January 12	1,260	6.4	1.842	50.78	
Total amount	4,095	....	7.182	98.24	
Daily average	1,024	5.98	1.7955	24.56	

The output of the child is estimated as urinary excretion (Table 2) and as fecal excretion (Table 3).

TABLE 2.—URINARY EXCRETION

	Amount, c.c.	Nitrogen, Gm.
January 9	275	0.67
January 10	400	1.0192
January 11	400	0.9520
January 12	500	1.2040
Total amount	1,575	3.8452
Daily average	393.8	0.9613

Large amount of bilirubin present.

TABLE 3.—STOOL EXCRETION (DRIED=61 GM.)

	Gm.
Nitrogen—	
Total for period	0.991
Daily average	11.89
Fat, per cent—	
Folin-Wentworth	77.95
Split fat (soaps and fatty acids)	22.6
Neutral fat	77.4
Fat, total amount	47.55
Daily average	11.89

Chemical tests of the stool were repeatedly negative for bile.

From a comparison of Table 1 with Tables 2 and 3, we are able to compute the absorption and the utilization of the food products (Table 4).

TABLE 4.—ABSORPTION AND RETENTION (DAILY AVERAGE)

	Nitrogen, Gm.	Fat, Gm.
Intake	1.7955	24.56
Output—		
Urine	0.9613	.....
Stool	0.2480	11.89
Absorption (from intestine)	1.5475 (86.2%)	12.67 (48.4%)
Retention (per cent. of intake)	0.5862 (32.6%)	.....

Weight of child during study was stationary.

It will thus be seen in this child, 10 weeks of age, that the nitrogen absorption from the intestinal tract and its retention in the body were but slightly, if at all, interfered with. A very marked disturbance in the absorption of fat from the intestine is noted. In contradistinction to the normal fat absorption of 88 to 96 per cent. (Rubner and Heubner,[1] Freund[2] and L. F. Meyer[3]), there is seen in this case an absorption of only 48.4 per cent. Not only is the absorption poor, but the splitting of the fat and saponification seem also to be interfered with. Thus Hecht[4] and Keller[5] offer from observations on normal and slightly pathological children, fat-splitting in the stool ranging from 88 to 90 per cent.

1. Rubner and Heubner: Ztschr. f. Biol., No. 38, p. 315.
2. Freund: Biochem. Ztschr., 1909, No. 16.
3. Meyer, L. F.: Biochem. Ztschr., 1908, No. 12, p. 422.
4. Hecht: Jahrb. f. Kinderh., 1905, No. 62, p. 612.
5. Keller: Monatschr. f. Kinderh., 1903, i, 234.

We may compare the findings in our case with the results of analyses offered by Niemann[6] in an instance of congenital absence of the bile-ducts with advanced biliary cirrhosis in a child of 9 months. Niemann notes a nitrogen absorption of 80 to 93 per cent. and a fat absorption of 28 to 39 per cent. During one period of his investigations, when the child was on a very low diet, more fat was found excreted in the stool than was ingested in the diet. Further analyses are not noted in his case.

3. Pancreatic Studies: It appeared of interest to us to further investigate this disease with a view of ascertaining the condition of the pancreatic secretion, its presence or absence from the intestinal tract, and if possible, the enzymatic potency of the elaborated ferments. This was undertaken by means of ferment analyses of the duodenal juice obtained by the Hess[7] method, and, second, by study of the ferments present in the stool and urine. The technic employed by Hess was followed closely, the duodenal catheter being passed two hours after the first feeding in the morning. During the course of one hour we obtained by aspiration 8 c.c. of slightly milky, cloudy material, of neutral reaction, containing much stringy mucus. This material was differentiated from the gastric contents by the strong acidity and increased milkiness of the latter.

The duodenal material was diluted with twice as much distilled water before testing. The stool was extracted in twenty-five times its volume of distilled water made slightly alkaline with sodium hydrate. Both materials were tested for pancreatic ferments in the following manner:

For amylase, by adding to 1 c.c. of the stool extract, urine or duodenal juice varying amounts of 1 per cent. starch solution and allowing this to incubate at 40 C.; the duodenal contents or urine was incubated for one hour, the stool contents for twenty-four hours (under toluol.). The persistence of starch was tested for by adding liberal excess of iodin solution.

For lipase, to 1 c.c. of material was added 1 c.c. of ethyl butyrate and 0.5 c.c. toluol; the whole made up to 25 c.c. volume, brought to exact neutral point (one drop of 1 per cent. alcoholic phenolphthalein solution as indicator) and incubated for twenty-four hours. The amount of acidity produced was titrated with N/10 NH_4OH; a boiled specimen served as a blank control.

Trypsin, Gross-Fuld method.

The following results were obtained:

Duodenal Contents:
Amylase—1 c.c. digests 9 c.c. of 1 per cent. starch solution in one hour.
Lipase—1 c.c. frees 0.1 c.c. of N/10 acid in twenty-four hours.
Trypsin—10 c.c. of 0.1 per cent. casein is digested by duodenal juice in dilution of 1:1,000 in twenty-four hours.

---

6. Niemann: Ztschr. f. Kinderh., 1912, No. 4, p. 152.
7. Hess: Am. Jour. Dis. Child., 1912, iii, 133; 1912, iii, 304.

We are not possessed of figures for the values of pancreatic ferments in duodenal contents of normal children. However, judging from the results obtained by one of us (Crohn) in normal adults (to be published) we are enabled roughly to deduce in this case (1) that the pancreatic ferments are present and therefore the pancreatic ducts are patent; (2) that the amylase and trypsin are strongly present; (3) that the lipase is very weak. This latter fact is the important fact, and is probably best explained by the absence of the normally present bile salts which act to increase the strength of the lipolytic ferment from ten to twenty times.

The examination of the urine for amylase, and of the stool for the presence of the three ferments, revealed the following:

TABLE 5.—RESULTS OF EXAMINATION OF URINE AND STOOLS FOR FERMENTS

	Urine	Stool		
	Amylase	Amylase	Lipase, c.c.	Proteose
Jan 9	Neg.	12.5 D. E.	0.1	
Jan. 10	100 T. D. E.	50 D. E.	.....	1:500 (casein)
Jan. 11	Neg.	.....	.....	Neg. (Mett; fibrin flakes)
Jan. 12	70 T. D. E.	.....	Neg.	1:62 (casein)

In order to appreciate the meaning of these findings several observations were made on infants a few weeks of age and in normal health. The results are given in Table 6.

TABLE 6.—FINDINGS IN NORMAL INFANTS

URINE: AMYLASE (TWENTY-FOUR-HOUR SPECIMENS)

A—1 c.c. urine digests 0.5 c.c. 1 per cent starch in 1 hour (200 c.c. total excretion) = 100 T. D. E.
B—1 c.c. urine digests 0 c.c. 1 per cent. starch in 1 hour = 0
C—1 c.c. urine digests 0 c.c. 1 per cent. starch in 1 hour = 0

STOOL: AMYLASE (EXTRACT = 2:50 DILUTION)

A—1 c.c. extract digests 0.25 c.c. 1 per cent starch in 24 hours=12.5 D. E.
B—1 c.c. extract digests 0 c.c. 1 per cent. starch in 24 hours = 0
C—1 c.c. extract digests 10 c.c. 1 per cent. starch in 24 hours = 250 D. E.
D—1 c.c. extract digests 1.5 c.c. 1 per cent. starch in 24 hours = 37½ D. E.
E—1 c.c. extract digests 0.5 c.c. 1 per cent. starch in 24 hours = 12 D. E.

STOOL: CASEIN TEST (GROSS-FULD METHOD. DILUTION 2:50)

Dilution

A—0.3 c.c. stool extract digests 10 c.c. 1 per cent. casein in 24 hours=1:825
B—0.01 c.c. stool extract digests 10 c.c. 1 per cent. casein in 24 hours=1:25,000
C—0.7 c.c. stool extract digests 10 c.c. 1 per cent. casein in 24 hours=1:357
D—0.3 c.c. stool extract digests 10 c.c. 1 per cent. casein in 24 hours=1:825

STOOL: LIPASE

A—0 c.c. acid produced from 1 c.c. ethyl butyrate in 24 hours.
B—0 c.c. acid produced from 1 c.c. ethyl butyrate in 24 hours.
C—1.9 c.c. acid produced from 1 c.c. ethyl butyrate in 24 hours.
D—0.1 c.c. acid produced from 1 c.c. ethyl butyrate in 24 hours.
E—7.1 c.c. acid produced from 1 c.c. ethyl butyrate in 24 hours.

In examining such findings in normal infants we are struck by the variability of the results in spite of an unvarying technic in carrying out the tests. Notwithstanding this, by comparison of the findings in the

pathologic case with those in normal controls we may note (a) that on two occasions strong amylase was present in the urine; (b) that a weak amylolytic ferment was present in the stools; (c) the proteolytic ferments of the stool, tested against casein, shows no diminution in the strength of this enzyme as normally present; (d) the lipolytic ferment, on the one occasion present, was very weak.

To do more than draw the most general conclusions from this scant data would lead to error. The question of the specificity of the ferments of the stool, and their relation to the diagnosis of pancreatic disease, must be reserved for a future discussion, as also the value of the casein test in the stool as an index of pancreatic-trypsin activity. However, in general, we may say that the pancreatic enzymes are present, and of normal strength, except the lipase of the stool, which, like the lipase of the duodenal secretion, is weak.

GENERAL CONCLUSIONS

From the study of this case of congenital absence of the bile-ducts, the conclusions are as follows:

1. Nitrogen metabolism is normal.
2. Fat metabolism is greatly disturbed, characterized by poor absorption and deficient splitting of neutral fats.
3. The pancreatic ducts are patent and the pancreatic secretion is of normal strength.
4. The lipolytic ferment of the pancreas, while present, performs its function weakly on account of the absence of the bile salts, which normally accelerate its enzymatic activity.

The authors wish to express their obligations to Dr. Samuel Bookman for helpful suggestions and material assistance during the course of this study.

ACUTE LYMPHATIC LEUKEMIA IN EARLY LIFE

AUGUST STRAUCH
CHICAGO

In 1857, under the title "A New Case of Leukemia," Friedrich[1] described a case in which the disease, interpreted by him as leukemia, ran an acute course with high fever, pronounced hemorrhagic diathesis and terminated fatally within a short time. After Friedrich, Ebstein in 1889 observed a similar case and collected from the literature sixteen analogous cases. On the basis of his own observations and of the collected material, he defined the clinical and pathologico-anatomic picture of this disease and represented the acute leukemia as a distinct entity. Since that time reports of this disease from various countries have been published, but from the relative scarcity of the literature, including the American, it seems that the disease is decidedly rare as compared with chronic leukemia.

Children are affected with relative frequency, especially the male. In this country Thomas McCrae[2] observed acute leukemia in a 3-year-old boy and collected thirteen cases in the first decade of life, some of them in America. Osler,[3] until 1901, reported from his hospital practice among thirty-four cases of leukemia, three running an acute course, all in young persons. Churchill[4] reported one case and collected fourteen cases of acute leukemia of childhood from the American and European literature subsequent to McCrae's report and gave brief abstracts of them; and Rosenberger[5] extended the collection from the literature.

After that we find very few additional reports of the occurrence of the disease in this country, mostly in adults.

In the last five years cases have been published by S. O. Sabel[6] and Satterlee, Proescher,[7] C. M. Emerson,[8] L. Lavenson,[9] Wynn[10] (girl 15 years old), Lichty,[11] J. M. King,[12] E. F. Cooke[13] (boy 9 years old).

1. Friedrich: Virchow's Arch. f. path. Anat., 1857, xii.
2. McCrae, Thomas: Bull. Johns Hopkins Hosp., May, 1900.
3. Osler: Practice of Med., 1901.
4. Churchill: Am. Jour. Med. Sc., October, 1904.
5. Rosenberger: Am. Jour. Med. Sc., 1904.
6. Sabel and Satterlee: New York Med. Jour., June, 1907.
7. Proescher: New York Med. Jour., Jan. 4, 1908, p. 9.
8. Emerson: Bull. Johns Hopkins Hosp., March, 1907.
9. Lavenson, L.: Univ. Penn. Med. Bull., July, 1909.
10. Wynn: Jour. Indiana State Med. Soc., February, 1908.
11. Lichty, M. J.: Cleveland Med. Jour., October, 1911.
12. King, J. M.: California State Jour., March, 1911.
13. Cooke: Virginia Med. Semi-Monthly, September, 1910.

Since some authors as Fraenkel[14] in Berlin, Bradford and Shaw[15] in England, Kovacs and Herz[16] in Vienna, Gilbert and Weil,[17] have seen several of such cases within a few years, we might assume that this affection is not quite as infrequent as one would infer from the relative scarcity of the reports. Evidently not all cases are brought to the knowledge of the profession, partly because on account of the similarity of acute leukemia to several other affections, especially in the absence of a hematologic examination, the disease has not been recognized but confounded with others.

With hemorrhages of the various organs often predominating, the clinical picture of acute leukemia, indeed, bears a striking resemblance to scorbutus or morbus maculosus Werlhofii, as, for instance, in the case of Osswald[18] (man), which only by the autopsy was cleared up; or to an hemorrhagic septicopyemic infection with anemia, or to malignant diphtheria, if necrotic, ulcerative processes of the tonsils with the formation of pseudomembranes are present, to which fact I later shall refer. There is no doubt that some cases of acute leukemia also have been mistaken for typhoid, due to the neglect of hematologic examinations.

Therefore, attempts at collecting more exact statistical data pertaining to the relative frequency of this morbid entity in the various countries would be futile.

The earliest occurrence of this disease was observed by Pollmann[19] in a new-born girl; mother's blood normal; baby sickly at birth, apathetic; petechiæ; at 16 days cyanosis; liver and spleen much enlarged, cervical and inguinal lymph-nodes somewhat enlarged. Temperature 101.8 to 106.7 F. Death at 19 days. Leukocytes 312,500. Post mortem: Leukemic changes, recent verrucous endocarditis of the tricuspid, pointing to an infection during fetal life. Additional cases of congenital lymphatic leukemia were observed by Siefart,[20] Saenger[21] and Lommel.[22] Acute leukemia in the senile age is described by Pineles[23] in a 73-year-old man.

SYMPTOMS

Similarly to an acute infection, the disease is associated with asthenia, pyrexia and other general symptoms. It runs a rapid course and terminates fatally within a period of a few days to several weeks, or,

14. Fraenkel, A.: Deutsch. med. Wchnschr., 1859.
15. Bradford and Shaw: Med. chir. Trans., 1899, lxxxi.
16. Kovacs and Herz: Wien. klin. Wchnschr., 1909, No. 14.
17. Gilbert and Weil: Arch. de méd. exper., 1899, p. 205; *ibid.*, 1904, p. 163.
18. Osswald: Correspondbl. f. schweiz. Aerzte, 1904.
19. Pollmann: München. med. Wchnschr., 1898, p. 44.
20. Siefart: Monatschr. f. Geb. u. Gynäk., 1898, viii, 215.
21. Saenger: Arch. f. Geburtsh. u. Gynäk., 1888, xxxiii.
22. Lommel: München. med. Wchnschr., 1905, No. 19.
23. Pineles: Wien. klin. Wchnschr., 1899.

exceptionally, a few months. The case of Guttmann,[24] lasting only four and one-half days, represents the shortest duration as yet reported. (Leukemia acutissima in a 10-year-old boy.)

The beginning of the acute leukemia can be either insidious or sharply marked, the former less frequently than the latter. In the first variety there are for days or weeks symptoms of a more general character, such as lassitude, weakness, pains in the neck or head, increasing pallor, shortness of breath on exertion, vertigo, febrile states or other vague forerunners of an impending disease, previous to the actual outbreak of the more outspoken, severe symptoms. Other cases set in with drawing pains in the extremities or with pains and swelling of the joints similar to articular rheumatism. Occasionally, the location of the prodromes or the first marked symptoms point rather directly toward a blood disease; thus several instances are known in which painful sensations in the splenic region ushered in the disease or violent epistaxis or hematemesis. Not infrequently hemorrhagic necrotic-ulcerative changes of the mucous membranes of the mouth, particularly of the gums and tonsils, or edema of the face, are the first symptoms.

On these symptoms supervene several features which are more apt to arouse a strong suspicion of acute leukemia, or at least of a severe affection of the hemopoietic system, viz., the appearance of hyperplasia of the lymphatic organs: the spleen, lymph-nodes, the lymphatic structures of the oropharyngeal cavity, of the thymus and the other lymph-adenoid tissues. But we must keep in mind the fact that the lymphatic tumors, although clinically rarely entirely wanting, may indeed be of insignificant degree and in the background of the morbid picture, even in the presence of a very pronounced lymphocytic blood-finding, the symptom diagnostically most important.

The tumefaction of the lymph-nodes never reaches such marked degrees as is seen in the chronic form of leukemia; it may be even very insignificant and more noticeable only toward the fatal termination; in other cases, on the contrary, the swelling may diminish again *sub finem vitæ*, simultaneously with an increase or decrease in the lymphemia.

Only in the minority is the spleen of normal size; the tumor, when present, is, in contradistinction to chronic leukemia, of a very moderate size, although very large spleens have been observed, especially in children, in whom a rapid enlargement during the short course of the disease was noted. It is remarkable also that the spleen-tumor may decrease before death.

The pharyngeal tonsils are enlarged in almost half of the number of cases, especially in childhood. Not infrequently they are the seat of

24. Guttmann: Berlin. klin. Wchnschr., 1891, No. 46.

ulcerations with necrosis of the lymphatic infiltrations, with hemorrhagic and diphtheroid exudate.

Sometimes there are spongy swellings, hemorrhagic ulcerations and necrotic conditions, with intense fetor similar to those of scorbutus in the mouth and pharyngeal cavities, which are exposed to traumas and other pathologic conditions (pharyngitis and gingivitis gangrenosa).

The most striking clinical manifestation of the disease is the hemorrhagic diathesis, expressing itself in hemorrhages into the general integument, the subcutaneous tissue, from the mucous membranes of mouth and nose, from the urogenital organs and the gastro-intestinal tract. Occasionally hemorrhages into the brain, muscles, nerves, retina, the labyrinth, with or without Ménière's symptom-complex, into the middle ear and acoustic nerve (G. Alexander) have been observed.

Gilbert and Weil[17] distinguished three principal types, according to the prevalence of the one or the other of the aforementioned principal symptoms:

1. The rare "typical" acute leukemia with enlargement of the lymphatic apparatus as the predominant feature.

2. The hemorrhagic form, characterized by an intense hemorrhagic diathesis.

3. The buccopharyngeal, i. e., the anginous and pseudoscorbutic form with hemorrhagic infiltrations and necrotic-ulcerative processes in the oropharyngeal cavity.

This symptomatic classification, however, must not be considered as fixed, since the diverse pictures may be more or less combined. Of practical importance is the fact that, in some cases, the hemorrhagic diathesis betrayed itself by a dangerous, even deadly, bleeding after adenotomy (Zarniko).

The symptom from which the name of the disease is derived and which diagnostically is most decisive, is the increase in the number of the white blood corpuscles in the circulation. The numerical increase concerns solely the lymphocytes and may reach very high figures, although moderate figures are the rule, if compared with chronic leukemia. The changes, however, of the blood-pictures in some acute cases, especially in the beginning, are only rudimentarily developed. The number of leukocytes is occasionally only slightly increased, indeed, even leukopenia can exist, as, for instance, in the case of Benjamin and Sluka[25] (2,500 per c.c.), of Jeanselme and Weil[26] (4,000 white blood corpuscles). In cases of very rapid course the increase may remain of a low degree; generally before death it rapidly reaches a high figure of leukocytosis. Thus the variation in the number of the leukocytes is considerable, ranging from

25. Benjamin and Sluka: Jahrb. f. Kinderh., 1907.
26. Jeanselme and Weil: Arch. gén. de méd., 1904, p. 511.

some hundreds of thousands, or less than 100,000 to below 10,000, with even leukopenia. The principal criterion, however, even with a low degree of leukocytosis, is the alteration of the leukocytic mixture, the relative increase in the number of the lymphocytes, often as high as 90 per cent. or more of the whole leukocyte count. This increase concerns as a rule the macrocytic forms. But in children not infrequently are the small forms of the lymphocytes numerically increased, an occurrence which otherwise in adults is as a rule met with only in chronic leukemia.

Occasionally the small and large forms are equally distributed, or in the beginning are the small, later the large forms prevalent. The number of the polymorphonuclear neutrophils constitutes almost always a very small percentage; in very few cases larger numbers of neutrophils were observed.

On the other hand, under the influence of intercurrent diseases, as pneumonia, otitis suppurativa, diphtheria or sepsis, the former leukemic state of the blood may become aleukemic. Chronic lymphatic leukemia in children has not yet been observed.

Observations of acute microlymphatic leukemia are recorded by Goldschmidt[27] (girl 16 years old), Forbes and Langmead[28] (child), Ogawa[29] (adult), Lovett Morse, Harry Low[30] (girl).

In the last years a series of well-observed cases became known in which in a pronouncedly acute course the blood-changes and the organs showed a myeloid character, so that the existence of an acute myeloid leukemia in children as well as in adults is an established fact. (Cases of Billings and Capps[31] (adult), Acuña[32] (child), Sternberg[33] (child), Hirschfeld[34] (adult), Grawitz (adult), etc.)

In atypical cases the differential diagnosis might be difficult; likewise in very young children, in whom, under normal conditions, a relative lymphocytosis exists, and sometimes myelocytes in a small number are to be found.

To complete the clinical picture in its main features other symptoms to be enumerated are the frequent enlargement of the liver due to lymphoid infiltration, almost regularly met with in early life, the progressive emaciation and cachexia, an increased excretion of uric acid, pallor of face and body with a peculiar wax-like tint due to a grave anemia, and, in most cases, fever. The latter is as a rule irregular,

27. Goldschmidt: Folia haematol., Berl., 1907, 655.
28. Forbes and Langmead: Proc. Roy. Soc., 1908, p. 129.
29. Ogawa: Ref. Folia haematol., Berl., 1906, p. 459.
30. Morse, Lovett and Low, Harry: Boston Med. and Surg. Jour., 1905.
31. Billings and Capps: Am. Jour. Med. Sc., 1903.
32. Acuña: Arch. de mal. des enf., 1906.
33. Sternberg: Wiener klin. Wchnschr., 1911, No. 47.
34. Hirschfeld: Berl. klin. Wchnschr., 1905.

moderate, interrupted by afebrile days, but sometimes typhoid or septic in its character.

Occasionally icterus of a hemolytic nature was observed. Lymphoid growths, clinically detectable, may occur also in the skin. These leukemic infiltrations (lymphomata) are, however, much rarer in acute leukemia than in the chronic form. In Lavenson's interesting case (adult) the whole body was covered by an eruption of nodules and papules in the skin, consisting of lymphocytic infiltrations; the overlying epidermis was in the older lesions necrotic; in others it formed bullæ. Such infiltrations are described also by Seelig[35] (boy), Hochsinger and Schiff[36] (child), Benjamin and Sluka (child), Litten.

Quite frequent are maculopapular, pustular and bullous exanthemata; they sometimes resemble lues, as in the case of Hitschmann and Lehndorf[37] (roseola leucaemica).

In a few cases the hemorrhages into the skin gave rise to necrosis and ulcerations by insufficient nutrition, trauma and infection of the skin.

Since the clinical picture as mentioned before may bear a resemblance to several other affections, thus often inviting interesting differential-diagnostic considerations and emphasizing the diagnostic importance of the hematology, and since an early recognition is of the utmost importance for the prognosis, I wish, by adding a contribution, to describe the following case of acute lymphatic leukemia in a child.

CASE REPORT

History.—K. W., 4 years old, son of a physician in Chicago, was always healthy until the fall 1910, when he suffered from acute tonsillitis with exudative patches, associated with high fever. There were repeated slight attacks the following winter, likewise with the formation of patches, which proved very persistent. The tonsils were always somewhat enlarged. He otherwise seemed in perfect health with unusually fresh and rosy cheeks and a lively disposition. About three and a half weeks before being first seen by me, the boy, to all appearances healthy, was sent to a summer resort in the state of Wisconsin. Here he is said to have had once or twice a slight fever; but more definite information was lacking. Three weeks later the child returned to Chicago. At this time the mother noticed that the color of his face was less fresh and healthy, although not pale, and that climbing stairs caused the boy to complain of fatigue and pain in the legs; he was losing appetite and liveliness. Suddenly fever supervened, the child became peevish and was brought to bed. I saw the patient the first time the following day, on June 29, 1911.

Examination (June 29, 1911).—Boy fairly nourished and developed, of a rather healthy color of face and general integument. Temperature 102 F., pulse 140.

The tonsils are slightly enlarged, reddened, with a few crypts covered with small yellowish-white patches. The spleen is enlarged; its lower pole, reaching during inspiration to the costal margin, is distinctly palpable and of a somewhat increased consistency. The liver is not enlarged, its lower border hardly reaching

35. Seelig: Deutsch. Arch. f. klin. Med., 1895, p. 537.
36. Hochsinger and Schiff: Vierteljahrschr. f. Dermatol., 1887.
37. Hitschmann and Lehndorf: Ztschr. f. Heilk., 1903, xxiv.

the costal margin. Both lower extremities, especially the anterior aspect of the legs, show a few spots of bluish, green and brown color in the otherwise normal skin. They are of about the size of a lentil, diffusely circumscribed and caused by extravasation of blood into the subcutaneous tissue. No petechiæ into the dermis. Over the heart area is a soft systolic murmur of hemic character. Several diarrheic dejections with mucus had occurred.

Course.—During the following days involution and resorption of the petechiæ took place with the usual changes in color, but a few new spots appeared daily, leaving behind pigmentations for a short time. The child was for two nights delirious. The temperature rose to 104 and dropped in irregular curves in about three days to subfebrile or normal. The stool became of normal appearance again but had a very offensive odor. The child seemed almost perfectly well again as far as the absence of subjective symptoms is concerned; he became cheerful, took interest in his play and regained a comparatively good appetite. But in spite of that, every day there still came a few hemorrhagic spots on the legs, and in still smaller number on the front of the thighs.

The spleen got larger and also the liver began to increase. The child's face and body became pale. No icterus. Over the right vena and bulbus jugularis a venous bruit was clearly audible.

On July 14 the examination of the blood gave the following result: Erythrocytes 2,200,000, good rouleau formation, no morphologic changes. Leukocytes, 40,000 per c.c.; large mononuclear cells, 32 per cent.; small mononuclear cells, 61.5 per cent.; polymorphonuclear cells, 6.5 per cent.

On July 22, after a period of a few days of normal or almost normal temperature and absence of subjective symptoms on the part of the child, on palpation through the emaciated, flabby subcutaneous fat tissue, a few lymph-nodes over the left clavicle were detectable, of the size of a hemp-seed to that of a small pea, not painful on pressure; also in the submaxillary regions. A few nodes in the right axilla were almost of the size of a pea, and in both groins a few nodes were larger than a hemp-seed. Every day appeared a few new hemorrhagic spots on the lower extremities; from now on also a very small number on the arms and over the whole trunk. No albumin was found in the urine.

July 24. Pallor pronounced, with a peculiar wax-like tint. Lips and mucous membranes of the mouth very pale.

Blood-examination: Erythrocytes, 2,056,000 (41 per cent.); leukocytes, 32,700; polymorphonuclear cells, 2 per cent.; large mononuclear lymphocytes, 54 per cent.; small mononuclear lymphocytes, 42 per cent., among them a few of intermediary size; eosinophils, 1 per cent.; basophils, 1 per cent.; myelocytes, 0 per cent. Normoblasts: One doubtful in several stained blood smears.

The lower border of the liver reaches the umbilical line; the spleen, of which the dull percussion sound begins in the midaxillary line at the eighth rib, reaches in the mammillary line downward almost to the umbilical line. From underneath the otherwise normal gum there ooze a few drops of blood between the upper incisors. In contrast to the objective symptoms of a rapid progress of the disease is the euphoria of the child, who is rather playful and good-natured much of the time.

July 25. The lower pole of the spleen reaches in the mammillary line to the umbilical line. The lower border of the liver stands about 1 cm. lower than yesterday. The lymph-nodes over the left clavicle are, in greater number, almost of the size of a pea, in the right axilla and in both groins a few grew larger than a pea. Daily a few additional bluish hemorrhagic spots are encountered in the subcutaneous tissue, diffusely circumscribed, from the size of a lentil to that of a finger-nail. Besides these deeper seated petechiæ there appear now minute, punctate purpuric extravasations into the dermis. Owing to the increasing anemia, the spots are of a very pale tint.

July 26. The child is peevish, becomes weaker and weaker, has lost all appetite and looks very ill; the sensorium is always intact. An injection of neutral salvarsan (0.12 gm.) into the gluteal musculature was made.

July 27. Over the right clavicle there are palpable lymph-nodes of the size of a hemp-seed to that of a pea. On the right side of the nape of the neck a gland increased to the size of a bean. The lymph-nodes of the other regions mentioned before show a slight advance in growth. The child is very weak, the conditions becoming rapidly worse, with moderate swelling and painfulness at the site of the injection.

July 28. The pain and swelling at the site of the injection have diminished. The boy has fallen away; prostration great.

July 30. Great prostration; every day there appear some new, very pale petechiæ beneath and into the skin. The lower border of the liver reaches 1½ inches below the umbilical line. The temperature of the last days was afebrile or slightly febrile and showed no noticeable influence of the salvarsan.

In the night from July 30 to 31 collapse, sopor, coma; loud shrieking in the comatose state; nausea and vomiting of a small quantity of blood immediately before death, which took place on July 31 at about 4 o'clock a. m.

Examination of Organs.—The microscopic examination of sections of tissue which I was permitted to take from liver, spleen and the site of the salvarsan injection, gave the following results (Dr. Maximilian Herzog):

The sections of the liver show an enormous interlobular cellular infiltration. The latter is so marked that the boundaries of the liver lobules are distinctly mapped out by powerful septa composed of the infiltrating cells, which surround the interlobular vessels in powerful columns. The infiltrating cells are characterized by a large, generally distinctly vesicular, or finely granular nucleus and only a moderate body of protoplasm. Polynuclear cells are very scanty in the cell masses described. These cells extend from the interlobular tissue into the lobule itself and they can be seen between the columns of liver-cells reaching to the very center of the lobule. However, the infiltration gradually decreases from the periphery to the center of the lobule. The liver-cells consist of a vesicular nucleus, rather poor in chromatin, and some nuclei, in fact, are nothing but a shell. The protoplasm of the hepatic cells is very much vacuolated.

The sections of the spleen exhibit tissue densely crowded with cells. The latter are packed so closely all through the sections, that the differentiation between the Malpighian corpuscles and the pulp spaces has become entirely effaced and the former can be recognized here and there only by the vessels they contain and by the relations of the latter to the trabeculæ. Open pulp-spaces can nowhere be distinguished. Practically all the cells seem to be mononuclear, with finely granular nuclei. Here and there a more vesicular nucleus is encountered. In the Malpighian bodies the proliferating center of Fleming is not recognizable. The splenic tissue is abundantly infiltrated with hematoidin granules.

The muscle from the site of the salvarsan injection shows inflammatory irritation, manifested by a considerable increase in sarcolemma nuclei, also inflammatory infiltration of the interstitial connective tissue. The infiltrating cells are both mononuclears and polynuclears; these in some places form rather wide strips between bundles of muscle fibers. One must, however, consider the possibility that these cellular infiltrations are due to the basic disease, i. e., the leukemia, because they appear very much like those cellular infiltrations seen in the parenchymatous organs. The striation of the muscle fibers, however, has become quite indistinct. The longitudinal lines can still be well recognized, but the transverse striæ have practically disappeared entirely. The sarcolemma nuclei and those of the infiltrating cells are well stained and do not exhibit those changes usually seen in necrosis. Hence it may be said that the muscles show the effect of inflammatory irritation and parenchymatous degeneration, but not of necrosis.

EPICRISIS

The foregoing case exhibits certain individual peculiarities. The onset of the clinical symptoms was rather sudden, with the picture of an

acute infection; however, the previous slight rise of temperature, the development of a certain degree of pallor, although only noticeable to the parents by comparison with the boy's former unusually healthy color, must be considered in the character of prodromes, which undoubtedly are to be brought in connection with the blood disease. The enlargement and increased consistency of the spleen noticeable at the time of the very onset of the acute manifestations point in the same direction.

Unfortunately, any information as to the time of the first appearance of the skin hemorrhages on the legs was lacking. The mother, when her attention was called to these pigmentations, referred them to traumatism (contusion). Such, indeed, was the aspect of the hemorrhagic patches.

It may be considered as very probable that in all cases of acute leukemia the actual onset of the affection precedes by some time the more marked, acute clinical manifestations, and that the disease merely was symptomless until then, or that the symptoms during this latent—sometimes perhaps only very short—period were not pronounced enough to be noticed. Considering the insignificance or the general and vague nature of the premonitory symptoms, such as fatigue, slight anemia or influenza-like attacks, which are suggestive of no special disease, especially not of a blood disease, it is, as Pinkus[38] points out, not strange that as yet few blood-findings of this prodromal stage are known.

However, that an early leukocytosis may be present is proved by a series of cases. Theodor,[39] for instance, observed a case in which a blood-count, the necessity of which was suggested by an intense epistaxis, revealed a high degree of leukocytosis, while the patient, a boy, 4 years old, otherwise enjoyed perfect health. In addition to this, in some cases blood-counts taken immediately after the onset of the symptoms revealed lymphatic leukocytemia. On the other hand, in a number of cases a short period before the marked onset of the disease and even during the initial stage, there did not yet exist any noticeable leukocytosis. Naegeli in his book mentions a case of apparent morbus maculosus Werlhofii, in whom the leukemic blood-changes took place not until during the agonal stage.

The clinical picture of our case in the beginning resembled somewhat an erythema nodosum or purpura simplex, accompanied by a tumefaction of the spleen and intestinal disturbances. However, the absence of infiltration and pain on pressure of the discolored hemorrhagic spots and of a hyperemic zone militated against erythema nodosum; the entire absence of typical sharply circumscribed small

38. Pinkus: Nothnagel's Spec. Pathol. u. Therapie, viii.
39. Theodor: Arch. f. Kinderh., 1897, p. 47.

petechiæ in the dermis, as we are used to encounter in purpura simplex (idiopathica), and the progressive enlargement of the spleen must have aroused the suspicion that we had to deal with a hemorrhagic diathesis, however slight, of a secondary nature, which, pointing to the blood, accentuated the necessity of an hematologic examination as the only criterion to the diagnosis.

With the exception of the moderate hematemesis *sub finem vitæ* the manifestations of the hemorrhagic diathesis, although present throughout the course of the disease, were of minor importance in the clinical picture. As mentioned before, the hemorrhagic diathesis in some cases controls the situation completely, expressing itself in very profuse epistaxis, extensive petechiæ and ecchymoses of the skin and mucous membranes, bleeding from the gastro-intestinal and urogenital tracts, that, without a blood examination, and in the absence of enlarged lymph-nodes, grave purpura hemorrhagica (morbus maculosus Werlhofii acutissimus) may be erroneously diagnosticated; or if a hemorrhagica stomatitis and gingivitis be predominant features in the pathologic picture, we may think we are dealing with scorbutus or Barlow's disease. M. E. Weill[40] describes acute leukemia in a 3-year-old boy which closely resembles Barlow's disease (leukocytes 412,000). Therefore, the great importance of hematologic examinations in all cases of hemorrhagic diathesis of obscure etiology suggests itself.

In my case, which I would class under the first of the three groups established by Gilbert, the liver and spleen during the period of observation proved the malignity of the process by their *rapid* enlargement from day to day to a degree not often met with in acute leukemia except in early life. In contrast to the objective findings was the comparative euphoria of the boy through the greater part of the course of the disease. A noteworthy enlargement of the lymph-nodes took place only during the last period of the malady and kept within very moderate degree, thus completing the typical picture of Gilbert's first group.

The tonsils, which in our patient had always been somewhat enlarged, were in the beginning only slightly inflamed. In mentioning this circumstance I point to the remarkable fact that acute tonsillitis is not infrequently encountered previous to the onset of acute leukemia, so that the assumption of the tonsils being in a series of cases the port of entrance for the virus, is not without clinical foundation.

On the other hand, the occasional necrotic-ulcerative processes of the tonsils due to the lymphoid infiltration in acute leukemia may give rise to a secondary septic infection, for which the disease acts as a good soil, and which not infrequently hastens the fatal issue. The destructive processes and pseudomembrane-like exudate of the tonsils may very

40. Weill: Semaine méd., 1906, No. 23.

closely resemble diphtheria, as, for instance, in the case described by Jeanselme and Weil concerning a 9-year-old boy, whose tonsillar affection associated with anemia and hemorrhagic diathesis was thought to be septic diphtheria and treated accordingly with antitoxin, until the blood examination revealed the true nature of the disease, viz., acute leukemia, which was confirmed by the autopsy.

Of special interest is the resemblance that some cases bear, particularly those without enlargement of the lymph-nodes, to typhoid fever, not only in many of the clinical manifestations—including intestinal hemorrhages—but also in the pathologic anatomy. Indeed, the intestinal lesions, the lymphoid infiltrations and ulcerations of Peyer's patches, are extremely suggestive of typhoid, and the anatomic differentiation apart from the bacterial findings between acute lymphatic leukemia and typhoid ulcers in the intestines is not rarely impossible, so that the microscopic examination of the blood and other organs must be resorted to, to determine the differential diagnosis.

These facts emphasize the necessity of making at the bedside repeatedly, at short intervals, exact blood examinations in all obscure diseases which in any way point to the blood, especially in hemorrhagic diathesis; the more so, since there have been observed cases which first presented an aleukemic state under the picture of a grave anemia, pseudoleukemia, etc., and rapidly developed increasing leukemic blood conditions only a few days before death. Waldstein (man), Koermoeczi[41] (woman), Senator (woman), Reichmann (girl), Litten, Mosler.

THERAPY

Induced by the fact that arsenic has displayed some therapeutic effect in chronic leukemia, pseudo-leukemia and other blood diseases of obscure origin, and also in septic infection (atoxyl, silver-atoxyl by Blumenthal, salvarsan by Lucksch[42]) I administered arsenic in the form of salvarsan in the dosage recommended by Bokay, who, in children, increased Ehrlich's dosage of 0.005 gm. *pro kilo* body weight to 0.088 — 0.01 *pro kilo* body weight. No effect on the course of the disease could be noted. With the exception of a transitory local reaction, no accessory clinical symptoms could be traced to the administration of salvarsan. A further examination to determine the character of the blood picture after the injection, was prevented on account of external causes. Treatment of liver and spleen of the child by the *x*-ray was tried twice, but was discontinued on account of the child's great excitement during the sitting. In the few cases of acute leukemia in early life in which roentgenotherapy was tried, no prolongation of life was observed, although very

41. Koermoeczi: Deutsch. med. Wchnschr., 1899, No. 15.
42. Lucksch: Wien. klin. Wchnschr., 1911, No. 20.

conspicuous effects were noted. After a latent period of a few days of a febrile reaction the leukocytes drop suddenly to normal or even subnormal figures; the lymph-nodes, spleen and liver diminish in size, the blood may even in the proportion of its corpuscular elements approach normal conditions—but all that does not avert the fatal issue. With a surprisingly rapid increase in the number of the leukocytes and the return of the increase of the size of the lymph-nodes, death occurred in all cases. (Cases of Churchill, Benjamin and Sluka, Studer,[43] Flesch.[44]) Unfortunately, the words of Gilbert and Weil hold true, that the physician has done his utmost in making the diagnosis, since this involves, as it seems, *quoad vitam* an absolutely bad prognosis.

ETIOLOGY

Little is known of the cause of acute leukemia. Some authors, as Benda, Banti and Ribbert, hold the view that the lymphatic form as well as the myeloid form of acute leukemia should be classified among the sarcomas; in fact, in a series of cases a general sarcomatosis of the lymphatic apparatus was observed. In Ogawa's case, for instance, of acute lymphatic leukemia there was a general sarcomatosis of the lymphatic apparatus, with the primary focus in the thymus, while in the kidneys, intestines, bone-marrow and bladder there were leukemic changes. But the majority of authorities have long inclined to refer the cause of leukemia, especially of the acute form, to infection, since the symptom-complex offers many parallels to the clinical picture of infectious diseases. The disease, however, seems to represent no etiologic unit. In a series of observations some infection, mostly tonsillitis or influenza, were the forerunners.

Turck,[45] who in four patients with "lympholeukemic reaction on acute infections" and general swelling of the lymph-nodes following tonsillitis (in one case also with enlargement of the spleen), observed recovery, is led to believe that there may exist a close genetic relation between an acute infection starting from the tonsils or the adenoid tissues of the oro-pharyngeal cavity and the acute as well as the more chronic forms of microcytic lymphemia.

Turck assumes that there exist forms of lymphatic leukemias of a known infectious origin, in which with the recovery from this infection the lymphemia—as in his cases—disappears and *restitutio ad integrum* occurs, while in the majority of the cases the etiology being unknown and the cause being irremovable, the patient succumbs. But there is no essential difference, and the nature of these processes is apparently one

43. Studer: Correspbl. f. schweiz. Aerzte, 1906, No. 4.
44. Flesch: Deutsch. med. Wchnschr., 1906, No. 16, p. 619.
45. Turck: Wien. klin. Wchnschr., 1911, No. 47.

and the same, the only difference being the issue. Luedke[46] observed the blood-pictures of acute lymphatic leukemia in a streptococcic septicemia; the patient recovered.

Sternberg expresses similar views as to the acute myeloid form. Recent authors, as Pappenheim, Naegeli, Hirschfeld and others, emphasize the fact that the blood-pictures in some cases of general bacterial infections are identical with those of acute myeloid leukemia, the only difference of the diseases being the issue. Sternberg quotes several instances in support of this statement from his own experience as well as from the literature. These cases represent general infections accompanied by changes in the blood and organs like those which are characteristic of acute myeloid leukemia. The changes possibly represent a biologic reaction of the hemopoietic organs on various non-specific, generally septic, infections which as a rule call forth a leukocytosis; under certain circumstances, however, a myelocytosis. Therefore, the differential diagnosis between these general infections and the acute myeloid leukemia may be impossible.

With increasing knowledge of cases of recovery such as the cases of "lymphatic reaction on acute infection," reported by Turck, or the much-quoted case of acute myeloid leukemia of Morawitz,[47] and with the interpretation of acute leukemia as a disease produced by various non-specific infectious agencies, we are perhaps justified in asking the question whether we should not qualify — however cautiously — our hitherto absolutely pessimistic prognosis, assuming a rare curable form of acute leukemia.

Among the different infections which may give rise to leukemic conditions, the pyogenic agents (streptococcus and staphylococcus) appear to prevail. (Cases of Erb,[48] *Streptococcus pyogenes longus* in lymphatic leukemia; of Ziegler and Jochmann,[49] *Staphylococcus pyogenes aureus*; of Herz,[50] *Staphylococcus pyogenes albus;* of Eppenstein.[51]) Proescher,[7] on the other hand, found spirochetes in the fluid obtained by aspiration from the lymph-nodes of a series of cases of acute lymphatic leukemia, pseudo-leukemia and lymphosarcoma, and was able to transfer a purely glandular affection to guinea-pigs by subcutaneous injection of an emulsion of one of the sarcomatous nodes. Sternberg succeeded in cultivating from the blood of two persons who died of acute myeloid leukemia *Streptococci pyogenes,* which inoculated into animals,

46. Luedke (quoted from A. Herz's Die acute Leukaemie, Leipzig und Wien, 1911, p. 161): Fortschr. d. Med., 1911, p. 793; Folia haematol. Berl., 1910, x, 9.
47. Morawitz: Deutsch. Arch. f. klin. Med., 1906-1907, lxxxviii, 493.
48. Erb: Deutsch. med. Wchnschr., 1907, No. 21.
49. Ziegler and Jochmann: Deutsch. med. Wchnschr., 1907, No. 19.
50. Herz, A.: Die acute Leukaemie. Leipzig and Wien, 1911.
51. Eppenstein: Deutsch. med. Wchnschr., 1908, No. 48.

produced the characteristic blood-findings of acute myeloid leukemia with myeloid changes in the spleen and bone-marrow.

Luedke, in Würzburg, obtained positive results in a healthy dog, in whom he repeatedly had inoculated an emulsion of fresh bone-marrow and spleen from a dog suffering from acute myeloid leukemia. By inoculating dogs and monkeys with *Staphylococcus albus* cultivated from leukemia in man, after previous anemization through injuring the hemopoietic organ-complex by pyrodin, he was able to produce leukemia-like blood-pictures in four cases. He obtained similar results by injecting mice with the spirochetes of recurrent fever.

Hirschfeld and Jakoby,[52] Ellermann and Bang[53] only quite recently succeeded in transmitting to healthy chickens a form of leukemia occurring in chickens. Also Pappenheim could produce leukemoid blood-pictures in chickens by saponin and ricin, after he had injured their bone-marrow by toluylendiamin, pyrogallol and pyrodin. On the other hand, Schridde obtained similar blood conditions in chickens by injecting simply extracts of various normal organs.

Of great importance seems to be the peculiar reaction of the blood-forming tissues, their disposition to the production of unripe forms of cells and their exhaustion of the power to form ripe cells, under the influence of toxic or bacterial stimuli. The myeloid metaplasias found, as mentioned before, in acute infections are possibly compensatory new formations of myeloid tissue, the bone-marrow being functionally extremely overtaxed or exhausted by the infection or intoxication. This toxico-infectious reaction may assume also a lymphadenoid character similar to acute lymphatic leukemia (Domarus[54]), as, for instance, exemplified by the liver lymphomata in typhoid and scarlet fever, and by the lymphadenoid metamorphosis of the bone-marrow observed by Reckzeh in young animals.

This peculiar disposition brought about in animals by experimentally injuring the hematopoietic organs may have its analogue in man in the effect of previous infectious diseases. In this way we may understand the fact, known long since, that certain diseases, as typhoid, malaria, chronic purulent infections, etc., are factors predisposing to leukemia.

A certain disposition of the lymphadenoid tissue to proliferate is present in childhood, at which time the lymphadenoid tissue shows an abundant development. Its intense activity expresses itself under physiologic conditions in the more intense washing-out of the lymphocytes into the circulation so that they may reach 70 per cent. of the white cells. The lymphatic tissue of children may react to pathologic stimuli

52. Hirschfeld and Jakoby: Berl. klin. Wchnschr., 1909, No. 7.
53. Ellermann and Bang: Zentralbl. f. Bakteriol., 46, 1908, xlvi, No. 7.
54. Domarus: Folia haematol. Berl., 1908, vi, 337.

more intensely than that of adults, as the observations in acute and chronic infections show. ("Lymphatic reaction.") So it is especially in childhood that lymphatic leukemia is prevalent, and in acute form, even not infrequently in its malignant aggressive type, while the myeloid form rather belongs to the subsequent periods of life, being very rare in childhood.

4557 Evanston Avenue.

ON THE CAUSE OF THE PERSISTENCE OF GONORRHEAL VULVOVAGINITIS IN CHILDREN

I. C. RUBIN, M.D., AND J. S. LEOPOLD, M.D.
NEW YORK

INTRODUCTION

The general disappointment encountered by most clinicians and specialists, with the therapy of gonorrheal vulvovaginitis in children, as well as the great diversity of opinions in regard to the possibility of ultimate cure of this infection in infants, have prompted us to make the present investigation. On the one hand, the disease is treated so lightly by some pediatrists that one is led to believe a case of gonorrheal vulvovaginitis can be cured in a very short while by a few applications of some antiseptic solution. While others assert that it may persist for eight or nine years and may be refractory to all treatment, and even last throughout a lifetime. (Epstein, Kakels, Cora Hamilton.)

The great diversity of opinion may be explained in several ways. (1) Observers have not had the opportunity to control their cases for a sufficiently long time. (2) The rules to determine whether a child is cured have not been established. (3) Insufficient attention has been paid to the anatomic and histologic structure and relations of the parts concerned. (4) Owing to the delicate construction of the parts, direct examination has not been practiced except in few instances.

To obviate these difficulties it was in the first place necessary to have material for study so grouped and isolated as to keep the patients under continuous surveillance for a number of years. Most of the cases in the literature have been concerned with ambulatory, non-dependable dispensary patients, or patients in hospitals designed for the treatment of acute cases only. It would seem, therefore, that children who are kept under observation for periods varying from one to six years would be best suited for the study. The number of cases investigated by us is fifty, all of whom have been under extended observation and under various treatment, including vaccine treatment.

Gonorrheal infection in adult females, as is well known, has a strong tendency to become chronic. For obvious reasons it is much more difficult to eradicate the disease in women than it is in men. For anatomic reasons the disease is apt to be more acute in children than in women and also more persistent. The parts involved are more susceptible in children because of the delicate epithelium of the vulva, vagina and urethra. In the adult female, the attack may start as a urethritis alone, or a vaginitis alone, and then spread in a descending or ascending direction. The

extension may, however, be curtailed by treatment. In the female infant or little girl, a very small quantity of gonorrheal pus may at the same time inoculate the urethra, vulva and hymen. The hymen does not form the effectual barrier that is maintained for it by some authors, as, e. g., Dudley. It is closed or atresic in very rare instances, and therefore cannot be expected to prevent the deeper invasion by the gonococcus infection toward the cervix. That this actually occurs in the great majority of cases has been proved by our investigation.

Most stress is usually laid on the vulvovaginitis. Few clinicians mention the status of the cervix, or the corpus, although some authorities (Scholtz) declare the cervix to be immune from attack, as opposed to conditions in adults. We suspected that this was not altogether true and that the infection is deeper and is lodged in parts not accessible to medication. With this end in view we determined to examine by direct inspection the cervix uteri in all children treated for gonorrheal vulvovaginitis. The direct method of electric lighted female urethroscope (Lowenstein) in three sizes was employed for the study. (It is well to mention that Kelly, Koplik, Bandler and others, had previously used a urethroscope with reflected light.)

It is interesting here to note that there are few accurate data in medical literature regarding the position, size and conformation of the cervix uteri or vagina in small children or infants. With the aid of the speculum it was possible to note the condition of the vagina and the vaginal portion of the cervix and the external os, under normal and abnormal conditions.

METHOD OF EXAMINATION

The urethroscope offers an excellent opportunity for the study of the cervix. Its application is easy. The little patient is placed in the dorsal position, with hips slightly elevated on a cushion or douche pan; both legs are supported by the nurse or attendant. It is preferable to use a small table, so that the nurse alone can control the patient. It is advisable not to exhibit the apparatus before the child. All preparations should be made so that the patient cannot see what is going on. After reassuring the patient the parts are gently cleansed. The proper size of urethroscope for the size and age of the child should be chosen. One should watch the straining efforts of the child, spread the labia and observe how wide the hymen opens. No lubricant is used, in order that the amount of pus may be accurately determined. Older children may be asked to bear down. The tube with obturator is introduced as far as it will go. This is often the full length of the instrument. Gradually it may be withdrawn until one of the cervical lips is encountered; the vaginal portion

may then be manipulated into the tube.[1] To determine the condition of the superficial part of the vagina, the instrument may be introduced slowly from just within the hymen till the cervix is reached. By this method we are also able to say exactly whether the cervix is or is not involved.

The examination itself is exceedingly easy. In some children one or several drops of blood, due to the abrasions of the eroded surface, may be marked. This is apt to occur when the little patient is restless or strains. The introduction of the instrument should not occasion trauma, pain or hemorrhage, provided the proper sized instrument is chosen. The size depends more on the patency of the hymen than on the caliber of the vagina, as the hymen is the more variable structure. The superficial examination of the vaginal introitus is scarcely sufficient to determine the presence of an infectious process, even if cultures are made, for there are remissions when pus is held back in the deepest portion of the vagina.

One of the first cases examined by us revealed the striking phenomenon that the condition of the vulvar orifice was by no means indicative of the amount of invasion. The following is a type:

A. C., aged 3 years, was sick two years and under treatment of various kinds. On inspection there was seen externally a moist vulvar orifice; there was not sufficient discharge to make a smear. In the vagina there were seen drops ot pus or muco-pus, scattered over various parts of both walls; occasionally a hemorrhagic spot, and almost invariably a smaller or greater collection of pus or muco-pus, in or around the cervix, the os being bathed in it.

In other instances, especially when pus was more abundant externally, the amount of pus in the deepest part of the vagina was proportionately large. *In the majority of these little patients the vaginal portion of the cervix seemed to bear the brunt of the infection.*

ANATOMIC FINDINGS

The Vagina.—In the majority of patients, the vaginal mucosa shows the columna rugae. The normal non-infected vagina is pink and is slightly moist. Under pathologic circumstances the appearance varies from a congestion, which may be scattered or general, to small hemorrhagic areas, and even small ulcerations. Occasionally there are small cryptic recesses or pockets containing a drop of pus, and here and there an occasional adhesion. The adhesions are usually associated with the crypt formation, and are most prominent at the vault of the vagina, or near the vaginal portion of the cervix. It is highly probable that stenosis of the vagina in the adult is a result of a similar, if not the same process.

In view of the findings in the vaginal mucosa, there can be no question of a true vaginitis. The vaginitis is indeed a constant lesion in the

1. The length of the vagina from the hymen to the vaginal portion of the cervix measures in children from 1 to 6 years from 1½ to 2¼ inches.

gonorrheal infection of children. The pathologic lesion in the vagina is, however, moderate in extent as compared to that of the cervix.

The Cervix.—The cervix normally varies considerably in shape and appearance. The size is fairly constant. We have noted that some children of 1½ years have as large a cervix as children of six years. This confirms Bayers' anatomic studies. It may be added further in this connection, that though the cervix in infants and small children equals, if not exceeds, the corpus uteri in size, it is poorer in blood-supply (Poirier). It is only at the menstrual epoch that the cervix takes on a greater blood-supply (Bayer). These anatomic facts are of significance in their bearing on the evolution of the disease, as well as on the effect of treatment.

Occasionally the anterior lip is very poorly developed and appears as a mere anterior ridge; while in some cases it appears hypertrophied and forms a distinct fornix. The posterior lip is usually the smaller. The cervix in the great majority of cases is directed backward; in some cases it appears to have a horizontal position. In the latter cases it is somewhat difficult to get the vaginal portion of the cervix into the field of vision. To succeed, the instrument is introduced as far as it will go and then tilted backward and forward. It may not be out of place in this connection to point out, that inasmuch as both walls of the vagina in the infant are in close contact, *a dimple appearing at the distal end of the speculum may be mistaken for the cervical os.*[2] This is particularly apt to be deceptive when pus or muco-pus is present.

While the surface epithelium of the portio vaginalis is in some instances smooth, a varying number of depressions are sometimes seen which resemble the scars of a multiparious woman. On the other hand, the same conformation which obtains in the vagina may be evident at the external os, and to an exaggerated degree. In the latter case the vaginal portion of the cervix presents a lobulated appearance.[3] In a few instances in which the mucosa was smooth, there was an ectropion of the cervical mucosa and posterior lip resembling an erosion as seen in the adult. Mucus and muco-pus are seen in the crypts, between the folds and covering a greater or lesser portion of the orifice.

The external os is of two varieties, (1) circular, (2) elliptical, or transverse. In either case it is a small aperture that admits of a very small probe. Only occasionally was the opening large enough to admit the point of a lead pencil. In no case was any attempt made to introduce a sound beyond the external os. Furthermore, it is not justifiable because

2. This has been observed in multiparous women when the Kelly speculum was used.

3. This condition sometimes persists in adult life. I have seen it in a married woman who consulted me for sterility. (I. C. R.)

the manipulation is necessarily a blind one and may result in the extension of the infection.

Infection of the Cervical Canal.—We have repeatedly seen pus and muco-pus escape from the external os after the vaginal portion was wiped clean by swabs. In some cases due either to treatment or to the mildness of the infection, deep inspection revealed only a bead of pus at an angle of a transverse-shaped external os, or a drop of muco-pus within the round orifice. In these cases cleansing of the vaginal portion failed to reveal an escape of discharge from deeper parts. In the few normal children we examined by means of the urethroscope we failed to find evidence of the so-called mucus plug within the cervix, as claimed by B. Wallace Hamilton. There was simply a slight amount of moisture of the vagina and of the vaginal portion of the cervix. With experience we could say definitely whether a child had gonorrheal infection without resorting to cultures.

In cases in which only a slight amount of discharge was found at the vulval orifice, and particularly around the clitoris, and where the microscopical examination simply showed detritus and epithelial cells and no true pus, deep inspection showed no inflammation. The discharge in these instances consists of sebaceous secretion, smegma and the products of uncleanliness. The presence of pus at the vaginal orifice may, as a rule, be taken to signify an inflammatory process involving deeper parts than are apparent to the naked eye. By means of the electric lighted instrument (female urethroscope), direct and definite evidence may be obtained of the vagina and the vaginal portion of the cervix, including the external os. This should be a requisite in the physical examination of children for the purpose of admission to hospitals and asylums.

PROGNOSIS AND TREATMENT

Asylum children and those kept in hospital wards run a more chronic course, owing mostly to repeated inoculation, and on account of their lower resistance. Where the epidemic embraces a score or more of children the treatment becomes a very difficult task. Not only the problem of isolation, but the time required to care for them make the chances for cure more remote. Children in private families have for this reason a better prognosis.

It is unnecessary to summarize all the therapeutic measures that have been employed to combat this disease. The various methods are described in the admirable article by Cora Hamilton. More recently serology has been drawn on in the hope of finding a specific cure. The reports on the results with the use of vaccines have been numerous; these, however, with few exceptions (B. W. Hamilton), are pessimistic.

The subjects of our inquiry have been submitted, in the past three years, to all known therapeutic remedies. There have been occasions

during the periods under which our little patients were observed when the energetic use of irrigations has been rewarded by the absence of discharge. The additional external application of ointment, for the associated dermatitis, also seemed to clear up the condition. This cure was, however, only apparent and temporary. When the children were allowed to leave the bed or when treatment was suspended the discharge returned. A similar experience was met with when yeast was used, either by suppository or by tamponade. Vaccines proved to be of practically no value, whether used alone or in conjunction with other measures.[4] It is no wonder that some observers have abandoned all treatment. Dr. Anna W. Williams, Rothschild and others, for instance, believe that rest alone can accomplish as much, if not more, than all other treatment. Rothschild urges that no local injection be used, but that at most one should cleanse the external genitals and give santal oil.

Rest is an undisputed factor in all treatment, but it cannot be wholly depended on to cure such an obstinate infection as gonorrheal vaginitis. We have shown that the infection involves the vagina and the vaginal portion of the cervix. Keeping the external genitals clean as the sole therapeutic measure, is obviously not to be recommended.

Realizing the general failure obtained by subcutaneous injections of antigonococcus serum and vaccines, we endeavored to procure a specific serum which should be applied locally instead of acting through the blood-stream. Through the kindness of Dr. M. Nicoll, Jr., we were able to employ a polyvalent antigonococcus serum in two cases. By means of the urethroscope we were able to introduce from 1 to 1½ and 3 c.c. of the serum which was retained by plain gauze packing. The packing was left in place for twenty-four to forty-eight hours, when it was changed and cultures were made both from the gauze and from the vaginal secretions. The result did not satisfy our expectations. Tamponade of the vagina is not an advisable procedure for the reason that the gauze acquires a foul smell. The serum proved to be an excellent medium for bacteria, without having the antibactericidal effect on the gonococci. In later treatment we simply poured the serum into the vagina by means of the urethroscope and only packed superficially. The children were also put back to bed in a moderate Trendelenburg posture in order to secure the retention of the serum. The results obtained by this change were no better.

It is not likely that vaccines or serums injected subcutaneously can ever have the anticipated good effect in the treatment of gonorrheal vaginitis in infants and children. On the other hand, serum applied locally must also fail, because it cannot reach the bacteria in the subepithelial tissues.

---

4. We are indebted to Dr. W. J. Wile of Ann Arbor, by whom the vaccine work was done.

These considerations at once indicate the necessity of a more active and a more persistent therapy, and this in general should be similar to the treatment of gonorrhea in the adult. A few suggestions derived from our study may be of help in the treatment of gonorrheal vaginitis.

1. It is important to determine the extent of the deep lesion before any active treatment is begun. For this purpose the electric lighted female urethroscope should be employed.

2. By means of the same instrument appropriate medication can be carried out.

3. When irrigations are resorted to the douche tip or catheter should enter the vagina at least 1½ inches.

4. Applications by means of swabs used alone are useless and injurious.

5. When strong silver solutions are applied to the cervix and vagina it is well to keep the patient in bed for a few days.

SUMMARY

From our investigation, the cause of the chronicity of the gonorrheal infection in children as compared to that in adults lies in several factors:

1. The invasion is more violent and more extensive owing to (a) the close proximity of the portals of entry; (b) the tender mucosa and epidermis.

2. Once started, the infection practically develops as in a closed tube. This is not due to the valve-like closure made by the hymen, but to the construction of the perineum, and the external and internal genitals. Each segment of the vagina from the most superficial to the deepest part serves as a valve to dam back the discharge. This is due to the fact that the vaginal walls are in close contact and do not permit of natural and easy drainage.

3. Crypts and adhesions in which bacteria lodge form in the vaginal mucosa.

4. The vaginal portion of the cervix shows the deepest changes and is at the same time in the most disadvantageous position for drainage and for treatment.

261 Central Park West—701 Madison Avenue.

A STUDY OF THE WASSERMANN REACTION IN CONNECTION WITH HEREDITARY SYPHILIS

L. R. DeBUYS, M.D.
Assistant Professor of Pediatrics, Medical Department, Tulane University
NEW ORLEANS

The high rate of infant mortality in the children of syphilitic parents is an element of great concern in the social problem, but even greater is the disaster caused by these children living to maturity with their condition unrecognized. How may these conditions be met? By adopting whatever means we can to determine the presence of syphilis, that it may receive prompt attention before the ravages of the disease are so great that the individual becomes a menace to society.

As an aid in determining the presence of syphilis in those cases presenting suspicious symptoms, it will be found that the serum diagnosis is of vast assistance. In the analysis of the symptoms in the cases of hereditary syphilis (to be referred to later) I found that by resorting to the Wassermann reaction a great many cases gave a positive reaction while not presenting a typical clinical picture of syphilis. These cases, however, had sufficiently suspicious symptoms to warrant corroboration, and in a great many of these cases positive reactions were obtained not only in the child, but also in the mother.

As there is much difference of opinion as to the reliability of the Wassermann reaction, I determined to satisfy myself with its study in connection with hereditary cases of syphilis.

The basis of this paper is the study of 244 Wassermann reactions in 235 cases, 9 of which were for either corroboration in diagnosis or control in treatment. The tests employed were the Tschernogubow and Noguchi modifications; of the former, 181 tests were made in 177 cases, and of the latter 63 tests in 58 cases. The 181 Tschernogubow tests were as follows: 123 positives in 120 cases, 70 in 70 parents and 53 in 50 children; and 58 negatives in 57 cases, 23 in 23 parents and 35 in 34 children. The 63 Noguchi tests were as follows: 33 positives in 28 cases and 30 negatives in 30 cases.

The Tschernogubow tests were made in all the parents, and in all the children of 3 years and above, while the Noguchi tests were made in all the children under 3 years of age.

In the 244 reactions, 156 were positive in 148 cases and 88 were negative in 87 cases. Of the 148 positive cases, 78 were children and 70 were parents, 61 mothers and 9 fathers. In only one of these cases,

a child, should the reaction have been different. This was one of twins. The other twin and mother each gave a negative reaction. As the patient was not brought back for a control reaction, it cannot be stated definitely whether the error was due to the baby or to the test.

In the 88 negative reports in 87 cases, 64 were children and 23 parents, 21 mothers and 2 fathers. A negative reaction was obtained in a baby 18 months old with a condyloma, from the scrapings of which treponema were found. In this instance also the baby did not return for a second Wassermann. This negative Wassermann cannot be explained except as an error. Aside from this case there were 8 instances in which there were irregular reactions, either a negative in the child and a positive in the mother, or the reverse. These cases have been classified as irregular and will be considered later.

Eighty-two specimens of blood from eighty-two mothers were examined, resulting in 61 positives and 21 negative. Eleven specimens of blood from 11 fathers were examined with the result that 9 were positive and 2 negative. In no instance in which the father's and mother's blood was examined was there any difference in their reactions. Eleven examinations were made; in 9 both were positive and in 2 both were negative. Seventeen children of these 11 fathers and mothers were examined with the result that 13 were positive, as were the parents, 2 were negative, as were the parents, and 2 were irregular. In the two instances classed as irregular the blood of the child did not give the same result as that of the mother and father, but in both instances the father and mother gave the same reaction. These two cases occurred in the same family.

Of 67 reactions made in mother and child (67 children of 53 mothers), 44 were positive in both mother and child, 14 were negative in both mother and child, and in 9 cases the results could be classed as irregular. The 9 include the 2 irregular results referred to in connection with the father and mother and child, and 7 the remaining irregular cases of this paper.

The blood of 29 mothers was examined without examining the child's blood: in 23 instances the result was positive, and in the remaining 6 it was negative. These results agreed with the clinical diagnoses of the children.

Of 142 children whose blood was examined, 78 were positive and 64 negative.

In 75 children, whose mothers' blood was not examined, the reactions were positive in 30 instances and negative in 45.

IRREGULAR REACTIONS

In 2 instances the father and mother gave a positive and the child a negative reaction; in 4 instances the mother gave a positive and the

child a negative reaction; and in 3 instances the mother gave a negative and the child a positive reaction.

Class A.—Father and Mother Positive; Child Negative

Cases 1 and 2 occurred in the same family. The negative reactions were not corroborated by further blood examinations and were made on the same day, so that the fault may have been with the Wassermann. The third child in this family gave a positive and was the one for whom I was first consulted. The history given by the mother was extremely suggestive of lues during her pregnancy with the two children in whom the negative reactions were obtained. Though the reaction may have been in error, it is possible that these two children may have been specific at birth, and were in an inactive state when their blood was examined. On the other hand, it must be remembered that a healthy child may be born of a specific mother. However, this is hardly the explanation in these cases, as the mother had active lesions early during both pregnancies.

Class B.—Mother Positive; Child Negative

Case 3. Negative reaction in a child 3 years old, the brother of a baby 7 months old with syphilitic epiphysitis. In this case the mother and baby were both positive.

Case 4. The eldest brother, age 6 years, of a marked case of congenital lues, and a member of a family in which father, mother, three sisters and two brothers gave positive reactions.

Case 5. A baby 5 months old who was in good health up to three weeks before being seen.

Case 6. A baby 8 months old.

In cases 3, 4, 5 and 6 the reactions should have been the same as those of the mothers. The failure to obtain such a result may have been due either to the child being in an inactive state of syphilis, or probably to the reaction.

Class C.—Mother Negative; Child Positive

Case 7. Baby 5 weeks old. Very suggestive history.

Case 8. Child 11 years old.

Case 9. One of twins 3 months old. Mother and other twin were negative.

In these cases it is difficult to explain the differences in the reaction except that probably the mothers were in an inactive state of syphilis, or that the children had acquired the disease since birth. In none of these cases, however, is a history of acquired syphilis given. It must again be remembered that the Wassermann might have been at fault. In Case 9 I am at a loss to explain the result.

Of course, in all these irregular cases several examinations should have been made before accepting an irregular reaction. This was not possible in any of these cases, with the exception of Case 4, in which two Wassermann reactions gave the same negative result. In Case 9 the disease may have been acquired, but no evidences were present for such a conclusion.

In analyzing 114 cases, 59 were males, 49 females and in 6 the sex was not stated; 61 were white, 45 colored and 8 not stated. Of these cases, 64 gave a positive and 50 a negative Wassermann reaction. The histories and symptoms varied considerably in the positive cases, from 54.9 per cent. of the cases having snuffles to 11 per cent. having fissures. The order of frequency was as follows: snuffles, nasal discharge, miscarriages and still births, syphilitic wig, enlarged liver, scaling palms and soles, restlessness and irritability, skin eruption, fontanels unusually large, digestive disturbances, enlarged spleen, wide separation of sutures, enlarged glands and fissures.

Of interest in the fifty negative cases was the infrequency of the symptoms of syphilis, but the presence in some cases of one or two of the symptoms sufficiently striking to require the exclusion of syphilis. Aside from 20 per cent. of these cases having nasal discharge and there being a history of miscarriage in 18 per cent., the frequency of suspicious symptoms ranged from snuffles in 16 per cent. to scaling palms, fissures, unusually large fontanel, wide separation of sutures and enlarged glands, each being present in 2 per cent. of the cases.

The history of syphilis in the parents was admitted in only two instances, but the regularity with which the mother and child reacted in the same way, and also the regularity with which the mother, whose baby's blood was not examined, gave a reaction agreeing with the clinical diagnosis of the baby shows that when the child was specific the mother had also had syphilis, though probably in a modified form.

The ages of the children in this study ranged from 12 days to 15½ years. Of these, 12 were from 10 to 15½ years; 30 from 6 to 10 years; and 100 under 6 years. Of the latter, 85 were under 3 years; 62 under 1 year; 48 under 6 months; 34 under 3 months; 24 under 2 months, and 4 under 1 month.

A marked symptom in the cases giving a positive Wassermann was their underweight: in 85 per cent. the underweight was from several ounces to several pounds.

CONCLUSIONS

1. The Wassermann reaction is a reliable means of diagnosis in hereditary syphilis.

2. In many instances, because of the difficulty to obtain the blood from a very small baby, an examination of the mother's blood will suffice for corroborative diagnosis.

3. Some of the symptoms found in syphilis may be found in non-syphilitic cases, and a negative Wassermann is of decided help in the elimination of syphilis in the diagnosis of these cases.

4. It is of interest to note that the blood of the father and mother react in the same way.

5. The law of Colle has again been disproved, because if a syphilitic child is born, the mother, though apparently healthy, is in reality not so, but has had syphilis in a modified form, proof of which can be shown by the Wassermann reaction.

A negative Wassermann does not exclude syphilis, as it may be obtained in cases before the antibodies appear in the circulation, or later when there is a temporary disappearance of the antibodies from the lymphatic and vascular systems due to the spirochetes being in lesions of fibrous character. A positive Wassermann, on the other hand, may be obtained in scarlet fever, leprosy, trypanosomiasis and scleroderma. However, with a very few exceptions other than the foregoing the constancy with which a positive Wassermann is present in syphilis and a negative Wassermann is present in cases not syphilis makes it, it must be admitted, a most valuable corroborative method of diagnosis, especially in cases not presenting a typical clinical picture of syphilis.

I desire to acknowledge my indebtedness to Dr. Frazer B. Gurd for the Wassermann reactions, which have made this paper possible.

1776 State Street.

PROGRESS IN PEDIATRICS

PROGRESS OF OPHTHALMOLOGY WITH SPECIAL REFERENCE TO DISEASES OF THE EYE IN CHILDREN

HOWARD F. HANSELL, M.D.
PHILADELPHIA

INTERSTITIAL KERATITIS

For many years it has been assumed that interstitial keratitis of children and young adults, that form characterized by slowly advancing and deep-seated opacity, beginning in or near the center as minute points, later joined to each other by streaks of opacity (the lymph-channels) and finally coalescing and spreading toward the limbus, accompanied by the formation of interstitial blood-vessels, was one of the symptoms of *inherited* syphilis. Recently it has been shown that this identical form of keratitis, differing not at all in its clinical manifestations except that the subjects had passed the period of puberty, can be caused by *acquired* syphilis.

Still more recently several authors, notably C. W. G. Brogan,[1] regard the diseases in some cases as tubercular in its origin. Brogan reports the case of a boy aged 11, who had suffered from tuberculous cervical glands and phlyctenular ophthalmia for eight years. Treatment by tuberculin (bacillary emulsion) was carried out for six months, beginning with a dose of 1/15,000 mg. and increased to 1/4,000 for the first two months; regular estimations of the opsonic index were made; afterward the treatment was regulated by clinical signs, an exaggeration of their intensity indicating a new dose. The cornea gradually cleared and vision improved. One who has treated many patients before the days of bacterial diagnosis may properly comment that the older therapeutics, atropin, hot water bathing, dark glasses, alterative tonics, fresh air, sunlight and attention to diet and other hygienic measures were frequently followed with equally good results both as to vision and duration of the disease, but in view of the causation, reliance on non-specific measures to the exclusion of tuberculin and salvarsan, is no longer justifiable. The injection of salvarsan, also, has shown much the same results as in other manifestations of syphilis in those cases in which the Wassermann test has been found positive. Yet too much confidence should not be felt

1. Brogan, C. W. G.: Ophthalmoscope, December, 1911.

in this remedy. It does not displace the old treatment but is only an adjunct to it.

Drs. Ziegler and deSchweinitz[2] commented favorably on its use in these cases. Dr. Ziegler's case is instructive. It was a typical example of hereditary lues in a boy 9 years old. The Wassermann reaction was strong + 4. He received an injection of 5 grains in 15 c.c. solution into the gluteal muscles. There was marked cellulitis with pain. The temperature rose to 102 F. and remained above normal for a week. The ocular improvement was noticable but did not meet expectations. One month later the Wassermann reaction was still + 4. An intravenous injection of 0.3 gram was given, and improvement was marked and rapid. In a month the Wassermann had fallen to a feeble plus, all local symptoms had disappeared, the corneal haze was clearing and vision had risen from *nil* to 6/200. He was then placed under the usual specific treatment.

Dr. de Schweinitz's patient had received three injections at intervals of a month with decided betterment of vision. He recommended that large doses of potassium iodid be given in the intervals between injections. "Prior to the use of the salvarsan, iodids and mercury had been given freely, without controlling the disease, for a period of nearly six months."

Seidel[3] treated twelve patients by the intravenous method in doses of .45 gr. to .50 gram, regulating the amount according to weight and strength of the children, followed in four or five days by a subcutaneous injection of .50 to .60 gram and after three to five weeks a second intravenous injection with perfectly satisfactory results. Lohleim[4] observed beneficial effects in nine cases, although he admitted that involvement of the other eye could not be prevented by the salvarsan.

Stoelp[5] in a study of 470 cases of eye diseases, among which were many of parenchymatous keratitis, reports a favorable influence of a single injection of salvarsan in 28 per cent. and no result in 72 per cent. of the corneal cases. Fleming[6] says in some cases of specific keratitis in children a decided influence was apparent in the rapid decrease of irritation but in others not the least.

L. Gersheimer[7] demonstrated the presence of the *Spirochaeta pallida* in a piece of tissue freshly excised from a parenchymatously diseased cornea of a girl 14 years of age who was positively suffering from hereditary syphilis. He says that the disease remained unaffected by salvarsan.

---

2. Ziegler and de Schweinitz: Tr. Ophth. Sec. Col. Physicians, Philadelphia, March 16, 1911.
3. Seidel: Arch. f. Ophthal., 1911, lxxix.
4. Lohleim: Wien. klin. Rundsch., May 7, 1911.
5. Stoelp: Klin. Monatsbl. f. Augenh., 1911, xlix.
6. Fleming: Arch. f. Augenh., 1911, lxviii, 197.
7. Gersheimer, L.: Wien. klin. Rundsch., Jan. 15, 1911.

The student of the ophthalmic literature of the past two years becomes confused by the conflicting opinions and by the contradictory testimony offered both as to the method of administration and the results.

Stephenson[8] ably and judicially sums up the latest conclusions thus:

> The gist of the whole matter appears to me to be that, when properly given, salvarsan presents no particular danger either as regards the body in general or the eye in particular. It has proved itself to be well-nigh a specific remedy in primary and secondary syphilis, and, furthermore, to act speedily and satisfactorily in some diseases of the eye, particularly in those of the uveal tract. There is no reason, therefore, why its employment in ocular maladies should not be extended and multiplied. Recent experience shows that it is best given by injection into the veins, and that the former one-time injection of small doses is not so efficacious as a series of from two to four injections, each of a maximal dose. In order that the action of one remedy may be supported and reinforced by that of another, Ehrlich's principle of so-called "combined therapy" should be adopted in diseases of the eye. In other words, each intravenous injection of salvarsan should be followed by a series of mercurial inunctions, the whole process extending over a period of from six to twelve weeks. The serum reaction should throughout remain our touchstone as to the efficacy of treatment and the permanance of cure. The continued absence of clinical manifestations has, it would seem, less value.

Tobias[9] believes that should parenchymatous miliary infiltrations develop, a tuberculous affection of the eye exists, even if other symptoms of local reaction, such as increased hyperemia, precipitates and opacities of the vitreous are lacking.

Another hypothesis, advanced by Columbo,[10] is that eczematous kerato-conjunctivitis is caused by the exudative diathesis, which may be considered to be a syndrome of symptoms characterized by intestinal troubles, affections of the skin, catarrh of the air passages, which in turn are produced by auto-intoxication from the intestines. This latter assumption must not be overlooked in determining the diagnosis of many eye affections, as well as general disturbances in children and in adults. The presence of urorosein or indican in the urine is almost a sure indication of auto-intoxication and indeed it may be frequently found in acne, eczema and the affections of the cornea and conjunctiva associated with them. As Bruns[11] says:

> It may not be always possible to get from these patients a history of gastro-intestinal derangements; but neither is it easy to elicit from the majority of them an account of any but the most striking illnesses. Disorders of the gastro-intestinal functions are perhaps with them so constant as to be regarded as a natural state of things and entirely normal. That a brisk purgation, preferably with a mercurial, and subsequent regulation of the bowels, is the measure favoring most the safe and rapid resolution of an attack, and that recurrence may be prevented by regulation of the diet and the withdrawal of certain articles of food, speak of the almost universal prevalence of gastro-intestinal derangements among phlyctenular patients.

---

8. Stephenson: Ophthalmoscope, Oct. 1, 1912.
9. Tobias: Klin. Monatsbl. f. Augenh., August, 1911.
10. Columbo: Klin. Monatsbl. f. Augenh., August, 1911.
11. Bruns: Tr. Sec. Ophth. Am. Med. Assn., 1912.

An interesting legal problem is presented by the traumatic origin of interstitial keratitis. A young person with inherited syphilis meets with an accident or receives a foreign body in the cornea and in the course of a few days' time parenchymatous keratitis—that form that has for years been considered as a characteristic of congenital, inherited or acquired syphilis—develops in that eye, runs its regular course and later, without traumatism or known outside cause, the same inflammation attacks the other eye. Several cases of this kind have recently been reported, and are authentic. Two occurred in 1912 among the patients of the out-patient eye department of the Jefferson Hospital, but fortunately no question of damages was raised in either case.

Von Hipple in 1906 contended that no positive proof had thus far been brought forward that traumatism could light up an interstitial keratitis.

Marx, in his Inaugural Dissertation, Zurich, 1909, collected from the German literature twenty-five cases.

Wicherkiewicz[12] adds three striking examples:

A boy of 4 with well marked stigmata of syphilis, inherited from the father, struck the right eye against a hanging lamp. A diffuse interstitial opacity accompanied by small epithelial blebs followed; recovery after usual treatment. Two months later typical inflammation of left cornea occurred.

A girl of 7, subject of inherited syphilis, had parenchymatous keratitis in both eyes following in second eye several weeks after an injury to the one eye.

In the third case the affection was lighted up in a tuberculous patient by an operation for congenital cataract.

The evidence is sufficiently strong to prove the sequence of traumatism and parenchymatous keratitis in a tuberculous or syphilitic patient. The important question at law is the responsibility and liability for damages.

The prevalence of syphilis as an underlying cause is shown by Beauvieux.[13] Among twelve cases he found positive Wassermann reactions in ten.

The diagnosis of hereditary syphilis cannot be complete according to Jopka[14] without ophthalmoscopic examination. Changes in the eye-ground are found in about two-thirds of the cases. They consist in haziness of disk and adjoining retina, scattered spots of exudation and a gray discoloration of the foveal region. Other common ocular signs are bluish discoloration of the sclerotic coats (affecting twenty-one out of

---

12. **Wicherkiewicz: Klin. Monatsbl. f. Augenh., January, 1912.**
13. **Beauvieux: Arch. d'ophth., October, 1910.**
14. **Jopka: Deutsch. med. Wchnschr., No. 12, 1911; Wien. klin. Rundsch., April 16, 1911.**

thirty-two members belonging to four generations of one family examined by Stephenson) interstitial keratitis, and affections of the uvea (chronic iritis and chorioiditis).

KERATOMALACIA

The cornea receives its nourishment from surrounding blood-vessels, having no vascularity of its own except pathologically. In impoverished states of the system it is one of the first tissues in the body to break down. Necrosis of part or all of the cornea means partial or total loss of vision. The affection is not infrequently found among infants when the food supply is insufficient or cannot be digested. That this disease exists only among children is disproven by several writers. One, Gann Labo, describes a similar destructive process of the cornea among negroes in Brazil under the name of Ophthalmia Brasiliana; among the Japanese as Kamme; and Wicherkiewicz[15] reports a case in an insane weaver aged 31, who suffered from religious delusions. He imagined himself to be a great sinner and as a sort of atonement for his crimes, ate only dry bread and potatoes and drank only water, although he worked hard during the day and spent whole nights in praying. From the resulting extreme emaciation of the body the right and then the left eye showed marked keratomalacia. Forced nutrition in the hospital arrested the destructive process of the less affected cornea. This improvement showed that the malnutrition was the most important etiologic factor of the disease.

EYE-STRAIN

Eye-strain is a comprehensive title for a group of symptoms originating in the application of a pair of normal, or nearly normal, eyes under conditions which increase the effort; for example, time, type, light or health or ametropia or heterophoria. It is not, as Bates[16] says, a disease, but is correctly stated by him as induced by a conscious (more frequently unconscious—H.) effort to maintain distinct vision. It manifests itself by more or less indistinctness of vision and by concomitant headache, dizziness, increased lacrimation, sensory symptoms, smarting, burning, itching or aching, a mildly inflamed condition of the conjunctiva and eyelids and various nervous disorders. Technically it is not a symptom of any form of inflammation of the eye. Symptoms which arise from inflammation are more or less characteristic of the disease and need not be mistaken for asthenopia.

PHLYCTENULAR CONJUNCTIVITIS

This easily recognized and usually non-dangerous disease of the conjunctiva is largely a disease of childhood, although it is not limited to

15. Wicherkiewicz: Postet. Okalist, 1910, No. 1.
16. Bates: Ophthalmology, January, 1912.

young people. It seems an indication of the general health, since it is seldom a purely local affection, or indication of eye-strain from an error of refraction. It is found most commonly in the so-called strumous or scrofulous children in association with gastro-intestinal disorders, enlarged tonsils, adenoids or chronic catarrh. At present it is generally believed to be due to the bacillus of tuberculosis or to its toxins, and in addition to the hygienic measures commonly resorted to is treated by tuberculin and bacillary emulsion. As Elschnig says, "In keratitis profunda (interstitial) one must always think of tuberculosis."

Stephenson and Jamieson[17] have tested twenty cases by the von Pirquet method and obtained a reaction in every case. Fifty per cent. showed obvious signs of tuberculosis and 75 per cent. gave a tuberculous history (Year Book).

TUBERCULOSIS OF THE CONJUNCTIVA

The recognition of this disease is attended with difficulties. Even the inoculation of guinea-pigs or rabbits by introduction of material taken from the conjunctival growths and the development of an inflammation (termed tuberculous) is not conclusive. While the severest laboratory test may not be absolutely reliable, clinically the signs resemble in one patient, trachoma, in another vernal catarrh, or Parinaud's conjunctivitis, in a third chalazion, so that there is ample excuse for divergent diagnosis. The tubercle bacilli have often been sought for but rarely if ever discovered. Dependence must be placed on enlargements of the glands, submaxillary or cervical, and the discovery of signs of tuberculosis of the lungs.

The peculiar flat non-pedunculated tumors of the tarsal conjunctiva, separated by apparently healthy tissue, of long duration, and subject to slight changes, are practically unmodified by any local treatment except excision. The recent reported cases include the following varieties: The flat outgrowths[18] inflamed chalazia and, in the lower lid, a small wedge near the free border of the tarsus protruding beyond it like a pouting lip in which small nodes could be seen:[19] chronic blennorrhea with scattered granulations in a girl who had been treated six years for trachoma;[20] ulcer on posterior half of the free border of the lid;[21] large cheesy ulcer involving the tarsus, miliary tubercles scattered over the conjunctiva of both lids and an isolated node at the limbus.[22]

---

17. Stephenson and Jamieson: Brit. Med. Jour., April 16, 1910.
18. De Schweinitz: Ophth. Rec., xix.
19. Koller: Arch. Ophth., xxxix.
20. Fainitzk: Viestnik. Ophth., xxvii.
21. Brown: Ophth. Rec., xix.
22. Proeller: Klin. Monatsbl. f. Augenh., April 10, 1912.

The affection is not a rare one when we consider that some cases may escape observation altogether and others are classified under other names. We believe the affection is more common than is usually supposed. In primary tuberculosis the importance of early recognition is of great value. By treatment metastasis may be prevented and the local disease cured. Just how long after the appearance of tuberculosis in the conjunctiva or in the eye-ball other organs of the body may be affected is not known. If one may judge of the history of primary and secondary syphilis, the incubation period is a short one, which statement warrants the opinion that every patient, promptly and energetically treated, both locally and generally, may be cured.

OPHTHALMIA NEONATORUM

The prevention and treatment of ophthalmia neonatorum are subjects of perennial interest. The Credé method of prevention—the instillation of a drop of 2 per cent. solution of silver nitrate into the conjunctival sac of the infant before infection has had a chance to get in its deadly work—that is, as soon as the head is born—and its many modifications, have been efficacious, and in all large hospitals and lying-in institutions have been adopted. In private practice it has never been popular and is frequently omitted, the physician trusting to the usual antiseptic cleansing. The disease has not been eliminated even in the hospitals where the Credé method is the routine practice, either through neglect of the attendant or the virulence of the poison. Among the very poor, and particularly when the infant is born out of wedlock, cases of ophthalmia are not infrequently seen in spite of the laws enacted by many of the states for its prevention.

Feingold[23] assumes for the average of the whole population a percentage of morbidity for ophthalmia neonatorum of at least 0.5 to 1 per cent. (Ophthalmic Year Book, 1911).

Of the substitutes for silver nitrate in the prevention, argyrol and protargol have had strong advocates and have been extensively used, principally because of the assumed damage to the cornea and the inflammation of the conjunctiva induced by the silver nitrate solution. The chemistry of these remedies has been studied by Pitzman[24] who says:

> We have two possible silver nitrate albumin mixtures. First, those in which silver nitrate is present in less amount than is required to satisfy the albumin affinity. Second, those in which silver nitrate is present in excess of the amount required to satisfy the albumin affinity. The first class, without excess free silver nitrate, are very poor germicides, killing staphylococci only at the end of twelve hours, but are antiseptics. The second class, with excess free silver nitrate, are powerful germicides. In the list of the silver albuminates at present in use

23. Feingold, M.: New Orleans Med. and Surg. Jour., May, 1910.

24. Pitzman: Tr. Ophth. Sec. St. Louis Med. Soc.. Dec. 6, 1911; Abstr. in Ann. Ophth., April, 1912, p. 431.

we have both classes represented. Argyrol and collargol are silver albuminates without excess free silver nitrate, hence are antiseptics but poor germicides. Albargin, ichthargan, novargan, etc., and most of the newer preparations, are silver albuminates plus excess free silver nitrate, hence are good germicides. As the second group contains excess free silver nitrate it does not appear reasonable that its members can have any real advantage over the simple solution of the nitrate of silver.

Bruns,[25] who has had a long and large experience in the principal eye hospital of New Orleans, adheres to the use of a 2 per cent. solution of silver nitrate. As to the value of argyrol as a prophylactic, his experience leads them to hope that it may prove its worth, but the statistics at hand are too small to be conclusive.

Gratkowski[26] states that in two years 1,519 infants were treated by sophol, 5 per cent. solution, and in only one instance was there ocular infection and this was late and due to maternal carelessness.

Moran[27] considers sophol the most convenient and satisfactory prophylactic yet produced.

Von Herff[28] has employed it on seventy-five hundred infants. In eleven hundred the mothers were affected with vaginal gonorrhea. There was not one case of early infection and but one of late. With sophol the reviewer has no experience. At a conference of the ophthalmic surgeons to the Philadelphia General Hospital it was agreed that the Credé method should be adopted and enforced. The result has been extremely satisfactory. Mild cases are very occasionally met with and severe ones almost never. Post[29] strikes the keynote of the whole subject when he says that the prophylactic treatment should be given by educating our boys and girls to lead clean, moral lives from their youth up; that women should demand of their husbands, not only that they are, but that they always have been, moral men, and that men should demand the same thing of those whom they will make the mothers of their children.

But little difference of opinion exists as to the efficacy of the following remedies: Cold compresses, potassium permanganate, argyrol 20 per cent., atropin or eserin, according to the condition of the cornea, and applications to the everted lids of silver nitrate, grains 1 to 10 to the ounce. Cold is to be substituted for heat after corneal involvement.

CONGENITAL CATARACT

The causative connection between rickets and the lamellar form of congenital cataract has been known for some years, but the relation of the so-called "blue sclerotics" to the same constitutional dyscrasia is new.

---

25. Bruns: New Orleans Med. and Surg. Jour., May, 1910.
26. Gratkowski: Year Book Ophth., 1911.
27. Moran: Va. Med. Semi-Monthly, April 22, 1910.
28. Von Herff: München. med. Wchnschr., xxxvii; Ophthalmology, lx, p. 432.
29. Post: Am. Jour. Ophth., xxvii, 257.

Two authors, Burrows[30] and Rolleston,[31] have described noteworthy illustrations. The former speaks of a family of twenty-nine persons in which thirteen, representing four generations, were afflicted with both abnormalities; the latter of a child 5 months old, a subject of hereditary syphilis, whose sclerotics were always blue, but variable in intensity.

Calhoun[32] calls attention to a cause for cataract in young people that has hitherto not been exploited, or at least has not received the attention it deserves. In 1904 his father, Dr. A. W. Calhoun, had two young patients from Florida who had serious "pernicious" anemia, were stunted in mind and body, and who had cortical cataracts. Their stools were loaded with the eggs of the *Ankylostoma duodenale*. The younger Calhoun reports two new cases. The first was that of an ignorant country lad aged 20 years, who stated that the left eye had gradually gone blind in the previous three months. He had been afflicted with hookworm for years. He was stunted in his growth, very pale, mentally dull and gave the appearance of a child of 12 years. He had a partial cataract in the right eye and a complete cataract in the left eye. After treatment for both affections, he developed mentally and physically and regained useful vision (20/70). The second and third cases were much the same. The hemorrhages from the retinal vessels observed and noted by other writers were also present in Calhoun's cases, and in one the conjunctival and not the retinal vessels were the source of the recurring hemorrhages.

MUSCLES

The importance of the early recognition and investigation into the causes of paralysis of the ocular muscles becomes apparent when we remember that these affections are not isolated or local but point with no uncertain finger to the involvement of the central nervous system. As a positive indication of general disease it is not inferior or of less value than hemiplegia, for example. The idiopathic or unexplained paralysis assigned to rheumatism or cold may be purely local and not symptomatic of any general trouble, but observation of the patient for months or years will often enable one to determine that they are the antecedents of spinal disease, particularly locomotor ataxia or of cerebral syphilis.

As sequels of diphtheria, paralysis of the ciliary muscle and of the sphincter iridis have long been known. The lesion, however, is not known. The nucleus may be the site of a minute hemorrhage or edema, or the radiating fibers from the ciliary and iris nucleoli may be in a state of inflammation from the action of the toxin.[33] Sydney Stephenson[34] has

30. Burrows: Brit. Med. Jour., January, 1911, p. 16.
31. Rolleston: Brit. Jour. Child. Dis., May, 1911.
32. Calhoun: Tr. Sec. Ophth. Am. Med. Assn., 1912.
33. Hawthorne: Ophthalmoscope, November, 1911.
34. Stephenson, Sidney: Clin. Ophthal., 1911, xvii, 573.

seen a number of cases of strabismus in infants and young children in polioencephalitis from which it is difficult to diagnose the ordinary functional internal strabismus.

The knowledge that such cases are not uncommon and may so readily be mistaken for those in which improvement if not restoration of binocular fixation may be brought about by treatment and operation, puts one on his guard before forming an opinion as to the value of glasses, atropin and operation. A little girl recently under my care is a case in point. When a few weeks old she had acute hydrocephalus and was in danger of death, or in the event of recovery, of paralysis. She recovered promptly and apparently perfectly after lumbar puncture. Internal squint was noticed at 6 months of age, too young for treatment. Recently the external rectus was advanced with improvement in her appearance, but with little prospect of her ever having binocular fixation.

In the treatment of the common form of internal strabismus, that due to the effort of accommodation to overcome hyperopia, the method advocated for years is successful and needs only to be emphasized. Prolonged therapeutic paralysis of accommodation by atropin, the wearing of as nearly a full correction as can be borne, and finally, and not until the other measures have been tried for months, advancement of one or both internal recti. For monocular squint, or those cases in which fixation is always made by the same eye, the other eye always squinting, the exercise of the amblyopic (squinting) eye by means of Worth's or other forms of amblyoscope is strongly recommended. Knowing, as we do, that destruction of the fixing eye will be followed by the development of the seeing power of the hitherto amblyopic eye, exercise and training of the retina and cerebral center of vision are sound in principle. It must be remembered, however, that the desired result can be attained only by the exercise on the part of the physician of great patience and perseverance.

SERUM AND VACCINE THERAPY

The progress of ophthalmology during the past year is nowhere better shown than in the valuable contribution to the subject of serotherapy made by Mayou.[35] For three years he has been studying on his own patients and on those of his colleagues in the Moorfield's Hospital, London, the effects of the injection of serum and vaccines on many ocular diseases. His paper is scientific and thorough and his conclusions represent the impartial testimony of an accurate observer. It must be read in its entirety to be appreciated. After an explanation and definition of the many terms used to designate the various bodies he gives his experience in brief as follows:

Styes.—Recurrent attacks due to infection of the glands about the lid margins, for which the vaccine treatment has been most frequently used,

35. Mayou: Ann. Ophth., October, 1912.

were most successfully treated. In all, thirty cases, the staphylococcus was found. The vaccine was a mixed cultivation of albus and aureus and as a rule three injections were given.

Acne Vulgaris.—Staphylococcus vaccine will frequently cure, although some cases recover only after injection of a vaccine made from a pustule on the face of the patient. Four cases associated with phlyctenular and corneal ulceration did not improve under the treatment any quicker or more certainly than they would have improved under local treatment with atropin and boric lotion. Multiple and recurrent chalazion should be treated by vaccine prepared from a cultivation made from the secretion rather than by a mixed stock vaccine.

Acute conjunctivitis of gonococcic or Koch-Weeks origin is as promptly relieved by the usual remedial measures as by vaccine. In these cases the sera are peculiarly suitable. The serum is injected into the tissues, usually the buttock and is also dropped into the conjunctival sac every hour.

Diphtheritic Conjunctivitis.—The beneficial results of the treatment by antitoxin are now placed beyond all doubt. The change becomes apparent in twenty-four hours, the temperature and pulse drop to normal and although there is some discharge from the eye the membrane shows signs of separation and it finally comes away piecemeal. If after another twenty-four hours the symptoms do not abate another dose of antitoxin should be given.

Staphylococcal Corneal Ulceration.—Four patients were treated by two injections of vaccine, five hundred million, eight days apart, with perfectly satisfactory results. In *pneumococcal* ulceration, if the serum contains the right strains of bacteria the results are brilliant. Four cases of tuberculous scleratitis were cured by tuberculin. This is usually an intractable and recurring disease and the result in these cases pretty clearly demonstrates both the etiology and the therapy.

Uveitis.—The organisms causing inflammation of the iris, chorioid and ciliary body, demonstrated to be present in the aqueous, are the tubercle bacillus, the staphylococcus and the *Spirochaeta pallida.* Of thirty cases, fifteen were tuberculous, ten staphylococcal and five syphilitic. "To summarize the results of treatment I should say that the method (injection of the tuberculin and sera) is a distinct advance in treatment, as yet far from perfect; that most of the cases are much benefited and occasionally brilliant results are obtained."

The abstract of Mayou's paper is incomplete, but is sufficiently long to convince the reader of the great value of his investigations and to instigate clinicians to take advantage of the microscopists' painstaking labors.

1528 Walnut Street.

INDEX TO CURRENT PEDIATRIC LITERATURE

BACTERIOLOGY AND PATHOLOGY

Adenitis, Cervical, with Special Reference to Roentgen-Ray Method of Treatment.—G. M. Dorrance.
Penna. Med. Jour., November, 1912.

Cancer in Children. (Maligne Tumoren im Kindesalter.)—W. Usener.
Deutsch. med. Wchnschr., Nov. 21, 1912.

Cirrhosis in Boy of Four Years.—G. R. Davis.
West Virginia Med. Jour., November, 1912.

Complement-Fixation Reaction, Application of, to the Diphtheria Group of Organisms.—M. E. Morse.
Jour. Infect. Dis., November, 1912.

Fetal Chondrodystrophy, Pathogenesis of. (Zur Pathogenese der Mikromelie.)—H. Abels.
Ztschr. f. Kinderh., Nov. 16, 1912.

Liver: Acute Yellow Atrophy in Child Three Years of Age.—F. Huber.
Arch. Pediat., October, 1912.

Purpura, Abdominal. (Henoch.)—A. Gara.
Jahrb. f. Kinderh., November, 1912.

Sarcoma of Kidney in Infants: Report of Case.—T. H. McCarley.
Jour. Oklahoma State Med. Assn., November, 1912.

Sarcomas, Primary, in Muscle.—F. Landois.
Berl. klin. Wchnschr., Nov. 25, 1912.

Thymus, Enlarged, Returns to Normal Size under Roentgen Rays; 3 Cases.—E. Albert-Weil.
Bull. Soc. de pédiat., October, 1912.

Urea in the Cerebrospinal Fluid in Infants.—Nobécourt, Sévestre and Bidot.
Arch. de méd. d. Enf., November, 1912.

METABOLISM AND NUTRITION

Acidosis, Histologic Determination of, in Inanition.—A. Nielsen.
Hospitalstid., Oct. 30, 1912.

Antibodies, Content in, of Normal Human Colostrum and Milk.—R. Tunnicliff.
Jour. Infect. Dis., November, 1912.

Breast-Milk in Infant Clinics. (Om Anvendelse af Ammer i Børnekliniken.)—C. E. Bloch.
Hospitalstid., Oct. 30, 1912.

Breast-Milk Nursing Pensions. (Stillprämien und ihre Erfolge.)—H. Risle and F. Schmidt.
Arch. f. Kinderh., Oct. 12, 1912.

Diabetes, Care of, in Child Eight Years of Age.—J. W. Thompson.
Mississippi Med. Month., November, 1912.

Fat in Stools, Simple Color Test for. (Eine einfache Methode das Fett im Stuhl färberischmikroskopisch nachzuweisen und quantitativ Abzuschätzen.)—L. Saathoff.
München. med. Wchnschr., Oct. 29, 1912.

Feeding, Artificial, Importance of, on Biologic Properties of Young Organism. (Einfluss von künstlicher Ernährung auf biologische Eigenschaften des Organismus in dessen frühem Alter.)—T. A. Ossinin.
Arch. f. Kinderh., Oct. 12, 1912.

Feeding, Infant, Graphic Chart Method of Studying and Teaching the Principles of.—David M. Cowie.
Am. Jour. Dis. Child., December, 1912.

Feeding, Infant.—L. Fischer.
New York Med. Jour., Nov. 16, 1912.

Feeding, Infant.—F. G. Crookshank.
Brit. Jour. Child. Dis., November, 1912.

Feeding, Long Interval, of Premature Infants.—J. C. Litzenberg.
Am. Jour. Dis. Child., December, 1912.

Feeding, Maternal.—J. P. Sedgwick.
Am. Jour. Obst., November, 1912.

Feeding of Premature Infants, Artificial.—J. Wyatt.
Jour. Obst. and Gyn., xxii, 1912.

Marantic Infant.—G. F. Little.
Am. Jour. Obst., November, 1912.

Milk, Experimental Studies on.—E. H. Schorer.
Jour. Infect. Dis., November, 1912.

Milk Depots, Infant.—R. G. Freeman.
Arch. Pediat., October, 1912.

Milk, Spray Method of Sterilizing. (Neues Verfahren zur Herstellung einwandfreier Trinkmilch.)—O. Lobeck.
Deutsch. med. Wchnschr., Oct. 31, 1912.

Milk, Study of Streptococci from, and from Epidemic Sore Throat, and the Effect of Milk on Streptococci.—E. C. Rosenow.
Jour. Infect. Dis., November, 1912.

Milk Supply.—C. Cristadoro.
Med. Rec., New York, Nov. 23, 1912.

Milk, the Neutral Red Reaction in.—E. Moro.
München. med. Wchnschr., Nov. 19, 1912.

Scorbutus, Infantile, Experimental Research on. (Moeller-Barlowsche Krankheit.)—C. Hart.
Jahrb. f. Kinderh., November, 1912.

DISEASES OF THE NEWLY-BORN

Facial Paralysis after Spontaneous Delivery. (Facialislähmungen nach spontaner Geburt.)—P. Carlsson.
Zentralblat. f. Chir., Nov. 2, 1912.

Imperforate Anus with Perineoscrotal Orifice.—G. H. Edington.
Brit. Med. Jour., Nov. 16, 1912.

Ophthalmia in New-born.—A. W. Tallant.
Am. Jour. Obst., November, 1912.

Rachitis in the Newly-Born. (Ueber Rachitis. III.)—M. Kassowitz.
Jahrb. f. Kinderh., October, 1912.

ACUTE INFECTIOUS DISEASES

Chorea, Acute, Salicylates in Treatment of, with Report of Nine Cases.—N. K. Fromm.
Albany Med. Ann., November, 1912.

Diphtheria and Leprosy, Spread of, by Human Stools. (Verbreitung der Diphtherie und Lepra durch die Faeces.)—E. Delbanco.
Deutsch. med. Wchnschr., Nov. 14, 1912.

Diphtheria Bacilli in the Lungs.—E. Reye.
München. med. Wchnschr., Oct. 29, 1912.

Diphtheria, Laryngeal, Clinical Diagnosis and Treatment of.—O. W. Hill
Jour. Tennessee Med. Assn., November, 1912.

Diphtheria, Laryngeal, Treatment of.—W. S. Farmer.
Jour. Tennessee Med. Assn., November, 1912.

Diphtheric Pseudotabetic Paralysis in Adult; Recovery under Antitoxin.—B. Auché and Dantin.
Jour. de méd. de Bordeaux, Oct. 13, 1912.

Measles and Urine, Toxicity of. (Harntoxizität und Masern.)—H. Mautner.
Deutsch. med. Wchnschr., Nov. 21, 1912.

Measles, Inunction Treatment of.—D. I. Connolly.
Practitioner, London, November, 1912.

Measles, Phagocytic Activity of the Leukocytes in.—R. Tunnicliff.
Am. Jour. Infect. Dis., November, 1912.

Meningitis, Case of.—E. A. Ross.
Lancet, London, Nov. 9, 1912.

Meningitis, Epidemic, Serotherapy of. (Behandlung der epidemischen Genickstarre durch Seruminjectionen in die Seitenventrikel. Bericht über einen geheilten Fall.)—E. Levy.
Arch. f. Kinderh., Oct. 12, 1912.

Meningitis, Pneumococcal Cerebrospinal, Case of.—J. H. Cumming.
Lancet, London, Nov. 9, 1912.

Meningitides, Various: Their Diagnosis and Treatment.—W. P. Lucas.
Arch. Pediat., October, 1912.

Noma Cured by Diphtheria Antitoxin. (Caso di guarigione del noma otténuta col siero antidifterico.)—G. Trotta.
Gazz. d. osp., Nov. 3, 1912.

Pertussis: Histologic Lesion in Respiratory Tract.—F. B. Mallory and A. A. Horner.
Jour. Med. Research, November, 1912.

Poliomyelitis, Anterior; Differential Diagnosis.—C. W. Negus.
Jour. Iowa State Med. Soc., Nov. 15, 1912.

Poliomyelitis, Experiments on Insect Transmission of Virus of.—C. W. Howard and P. F. Clark.
Jour. Exper. Med., December, 1912.

Rheumatic Infection, Avenues of.—W. P. S. Branson.
Brit. Med. Jour., Nov. 23, 1912.

Rheumatism, Acute, with Subcutaneous Nodules in Children. (Rheumatismus nodosus im Kindesalter.)—R. Berkowitz.
Arch. f. Kinderh., Oct. 12, 1912.

Rheumatism in Children.—J. F. Dunn.
Kentucky Med. Jour., November, 1912.

Scarlet Fever, Cell Inclusions not Pathognomonic. (Sind die Einschlüsse in den polynucleären Leukocyten bei Scharlach als pathognomonisch zu betrachten?)—H. Bongartz.
Berl. klin. Wchnschr., Nov. 4, 1912.

Scarlet Fever, Intraleukocytic Bodies in.—D. J. Glomset.
Jour. Infect. Dis., November, 1912.

Scarlet Fever, Leukocyte Inclusions in. (Ueber die Döhleschen Leukozyteneinschlüsse bei Scharlach.)—M. Kretschmer.
Deutsch. med. Wchnschr., Nov. 14, 1912.

Whooping-Cough.—H. C. Buck.
Mississippi Med. Month., November, 1912.

Whooping-Cough. (Alcune considerazioni sulla tosse convulsiva.)—A. Dellepiane.
Gazz. d. osp., Nov. 3, 1912.

Whooping-Cough, Treatment of.—J. B. Bilderbach.
Northwest Med., November, 1912.

TUBERCULOSIS AND SYPHILIS

Hip-Joint Disease, Short Spica in Treatment of.—C. R. Keppler.
Am. Jour. Obst., November, 1912.

Pneumothorax, Artificial, in Pulmonary Tuberculosis.—C. Saugman.
Hygiea, Stockholm, October, 1912.

Thorax, the Build of the, and Pulmonary Tuberculosis. (Thoraxbau und tuberkulöse Lungenphthise.)—C. Hart.
Med. Klin., Nov. 24, 1912.

Tuberculin in Childhood, Cutaneous Reaction to.—C P. Lapage.
Brit. Jour. Child. Dis., November, 1912.

Tuberculosis Among Children, Modern Combat Against.—Nietner.
Lancet, London, Nov. 16, 1912.

Tuberculosis in Children.—T. V. Keene.
Jour. Indiana Med. Assn., Nov. 15, 1912.

Tuberculosis, Laryngeal, in Children.—Collet.
Lyon méd., Oct. 27, 1912.

Tuberculosis, Laryngeal, Neurotomy to Relieve Pain in. (La neurotomie du nerf laryngé supérieur dans la dysphagie des tuberculeux.—A. Chalier and P. Bonnet.
Presse méd., Nov. 9, 1912.

Tuberculosis, Phases of, in Relation to Immunity: Prevalence, etc. (Tuberkulosens stadier og immunitetsforhold.)—K. F. Andvord.
Norsk Mag. f. Lægevidensk., November, 1912.

Tuberculosis, surgical, in Children, Tuberculin Treatment of.—C. Förster.
Beitr. z. Klin. d. Tuberk., Nov. 9, 1912.

Tuberculous Infection and Tuberculous Disease in Infancy and Childhood.—C. P. Lapage.
Brit. Med. Jour., Nov. 16, 1912.

Tuberculous Disease of Joints, After-Results of Major Operations for.—H. J. Stiles.
Brit. Med. Jour., Nov. 16, 1912.

Tuberculous Joint Disease, Use of Carl Spengler's "I. K." Serum in Treatment of, with Report of Cases.—H. O. Eversole and C. L. Lowman.
Am. Jour. Orthop. Surg., November, 1912.

GASTROINTESTINAL SYSTEM

Appendicitis in Infancy and Early Childhood.—C. G. Cumston.
Med. Rec., New York, Dec. 7, 1912.

Appendicitis in Inguinal Hernia in Infant.—J. Becker.
Arch. f. Kinderh., Oct. 12. 1912.

Diabetic Boy of 8. (Exposé d'un cas de diabète infantile.)—P. Merklen.
Bull. Soc. de pédiat., October, 1912.

Duodenum, Congenital Occlusion of.—E. M. Cowell.
Quart. Jour. Med., April, 1912.

Duodenal Ulcer in Infants. (Zur Diagnose und Pathogenese des Duodenalgeschwürs im Säuglingsalter.)—H. Flesch.
Jahrb. f. Kinderh., November, 1912.

Dyspepsias of Childhood after Period of Infancy.—R. Hutchison.
Brit. Med. Jour., Nov. 16, 1912.

Helminthiasis in Children.—W. W. Murphy.
Am. Jour. Dis. Child., December, 1912.

Pancreatitis with Jaundice in Infectious Diseases.—W. L. Goldie.
Lancet, London, Nov. 9, 1912.

Pylorospasm.—W. M. Taylor.
Jour. Oklahoma State Med. Assn., November, 1912.

Sugars and High Percentage of Proteids, Effects of, on Fermental Disorders in Children.—W. Weston.
Jour. S. Carolina Med. Assn., November, 1912.

Teething, Is Any Illness in Infants Due to?—F. S. Hone.
Australasian Med. Gaz., Oct. 19, 1912.

RESPIRATORY SYSTEM

Bacteria Involved in Diseases of the Respiratory Apparatus in Children. II.—G. Brückner, W. Gaehtgens and H. Vogt.
Jahrb. f. Kinderh., October, 1912.

Bronchitis, Chloromatous.—H. Lehndorff.
Ztschr. f. Kinderh., Nov. 16, 1912.

Empyema in Infancy, Report of Case.—J. M. Brady.
Jour. Missouri Med. Assn., November, 1912.

Pulmonary Fibrosis in Children.—C. Miller.
Practitioner, London, November, 1912.

Pyopneumothorax and Pleural Gurgling. (Pyopneumothorax et bruit du glouglou pleural.)—J. Renault and P. Lévy.
Bull. de la Soc. de Péd., October, 1912.

Respiratory Metabolism in Proportion to Surface Area of Infants. (Atrophie und respiratorischer Stoffwechsel.)—A. Schlossmann.
Ztschr. f. Kinderh., Nov. 16, 1912.

Tracheotomy, Low, Technic for. (Die stumpfe untere Tracheotomie mittels Schielhäkchen.)—R. Dobbertin.
Deutsch. med. Wchnschr., Oct. 31, 1912.

Bronchial Glands, Enlarged, Diagnosis of.—Henry Farnum Stoll.
Am. Jour. Dis. Child., December, 1912.

Pediatrics, Progress in, of the Respiratory System.—B. S. Veeder.
Am. Jour. Dis. Child., December, 1912.

Serum Treatment of Pneumonia.—R. G. Freeman.
Am. Jour. Dis. Child., December, 1912.

CIRCULATORY SYSTEM

Anemia of Alimentary Origin.—A. Czerny.
Ann. de méd. et chir. inf., Oct. 15, 1912.

Anemia in Infants.—L. Tixier.
Ann. de méd. et chir. inf., Oct. 15, 1912.

Hemophilia Neonatorum in Family of Four Infants.—R. L. Pitfield.
Arch. Pediat., October, 1912.

Varices, Congenital.—C. Boisse.
Jour. de méd. de Bordeaux, Oct. 27, 1912.

NERVOUS SYSTEM

Amaurotic Idiocy, Family, Case of Juvenile Form of.—H. Gifford.
Ophth. Rec., November, 1912.

Amaurotic Idiocy, Two Cases of.—V. Magnus.
Norsk Mag. f. Lægevidensk., November, 1912; also Hospitalstid., November, 1912.

Brain in Infant, Entire Softening of. (Fall von totaler Erweichung beider Grosshirnhemisphären bei einem 5 Monate alten Kinde.—E. Meier.
Jahrb. f. Kinderh., November, 1912.

Bulbar Palsy, Acute, Case of, with Autopsy and Histologic Findings; Type; Anterior Poliomyelitis.—A. Wiener.
Med. Rec., New York, Dec. 7, 1912.

Chorea, Hereditary, Six Cases of.—E. P. Ballentine.
New York State Jour. Med., November, 1912.

Convulsions in Children, Relation of, to Dietary Errors.—J. B. Jackson.
Jour. Michigan Med. Soc., November, 1912.

Dura Mater, Rupture of, During Delivery. (Om Bristninger i Dura mater opstaaede hos myfødte under Fødslen.—L. Meyer and E. Hauch.
Hospitalstid., Nov. 6, 1912.

Feeble-Minded and Backward Children.—R. Roth.
Australasian Med. Gaz., Oct. 12, 1912.

Feeble-Minded and Delinquent Children, Association in.—F. C. Eastman and A. J. Rosanoff.
Am. Jour. Insan., July, 1912.

Feeble-Minded Children, Education and Training of, in Public Schools.—A. W. Edson.
New York Med. Jour., Dec. 7, 1912.

Feeble-Minded, Need for Educating Public Opinion on Problem of.—M. Booth.
Australasian Med. Gaz., Oct. 12, 1912.

Heredity in Mental Diseases, Some Problems in.—H. A. Cotton.
Am. Jour. Insanity, July, 1912.

Mental Defectives.—A. Davidson.
Australasian Med. Gaz., Oct. 12, 1912.

Mental Defectives.—E. Sinclair.
Australasian Med. Gaz., Oct. 12, 1912.

Myasthenia Gravis.—A. M. Starr.
Jour. Nerv. and Ment. Dis., November, 1912.

Myelitis, Acute Infectious Transverse, Due to Virus of Poliomyelitis; Complete Recovery.—B. Sachs.
Jour. Nerv. and Ment. Dis., November, 1912.

Myatonia Congenita.—M. Berihardt.
Jahrb. f. Kinderh., November, 1912.

Myotonia (Thomsen's Disease).—T. W. Griffith.
Quart. Jour. Med., January, 1912.

Psychasthenia, Juvenile, Cases of, Illustrating Successful Treatment.—T. A. Williams.
Am. Jour. Med. Sc., December, 1912.

Psychogenic Disturbances in Children. (Ueber den Mechanismus psychogener Erkrankungen bei Kindern.)—F. Hamburger.
Wien. klin. Wchnschr., Nov. 7, 1912.

Reaction of Degeneration, Distant. (Klinische Bedeutung der "Fernreaktion auf Entartung" von Ghilarducci.)—V. Forli.
Med. Klin., Nov. 17, 1912.

GENITO-URINARY SYSTEM

Foreign Bodies in Bladder of Girl Infants. (Ueber Harnblasenerkrankungen bei kleinen Mädchen durch bisher nicht beobachtete Fremdkörper.)—H. Abels.
Wien. klin. Wchnschr., Nov. 14, 1912.

Genital Organs in Little Girls, Displacement of. (Dystopie der inneren Genitalien bei Mädchen im frühen Kindesalter.)—J. Vas.
Jahrb. f. Kinderh., November, 1912.

Hydronephrosis, Congenital, with Aplasia of Ureter.—F. Van Der Bogert.
Arch. Pediat., October, 1912.

Kidney and Ureter, Clinical Diagnosis of Congenital Anomaly in.—W. F. Braasch.
Ann. Surg., November, 1912.

Kidney, Congenital Displacement of. (Fall von Nierendystopie.)—A. G. Lukina.
Ztschr. f. Urol., November, 1912.

Kidneys, Cystic, in Infant.—W. A. Fraser.
Australasian Med. Gaz., Oct. 5, 1912.

Nephrolithiasis, Infantile Kidney and Occlusion of Ureter with, on the Opposite Side.—J. S. Lewis and C. W. Bethune.
Am. Jour. Urol., November, 1912.

Uremia in Infants. (La form somnolente de l'azotémie du nourrisson. Son diagnostic avec la méningite tuberculeuse.)—P. Nobécourt and Maillet.
Bull. Soc. de pédiat., October, 1912.

Ureter, Congenital Stricture of, Producing Pyonephrosis; Nephrectomy.—L. M. Kahn.
Med. Rec., Nov. 16, 1912.

Urethra, Congenital Double, Case of.—W. Lenehan.
Am. Jour. Urol., November, 1912.

OSSEUS SYSTEM

Arthritis, Rheumatoid, Case of, in Child Six Years of Age.—W. R. Jordan.
Brit. Jour. Child. Dis., November, 1912.

Femoral Heads and Necks, Bony, Absence of.—J. Ridlon and H. B. Thomas.
Am. Jour. Orthop. Surg., November, 1912.

Fracture, Non-Consolidating, Treatment of.—C. Bertolotti.
Policlinico, Rome, Nov. 17, 1912.

Hip, Pathology and Therapy of Congenital Dislocations of.—R. Werndorf.
Am. Jour. Orthop. Surg., November, 1912.

SKIN AND APPENDAGES

Skin, Marbling of, in Children. (La livedo chez les enfants.)—J. Comby.
Arch. de méd. d. Enf., November, 1912.

Trichophytosis, Specific Extracts of Parasites in Treatment of.—R. O. Stein.
Wien. klin. Wchnschr., Nov. 14, 1912.

EYE, EAR, NOSE AND THROAT

Blindness as Result of Inflammatory Disease, Affecting Conjunctiva and Cornea.—C. W. Cutler.
Arch. Pediat., October, 1912.

Cross-Eyes in Children, Treatment of.—F. A. Kiehle.
Northwest Med., November, 1912.

Mastoid Region in Infants, Inflammation of; Five Cases.—M. Zæpffel
Rev. mens. de gynéc., d'obst. et de pédiat., October, 1912.

Nose and Throat, Care of, in Children.—H. Hays.
Am. Jour. Obst., November, 1912.

Ophthalmia Neonatorum, Duty of Practitioner in Cases of.—S. Stephenson.
Lancet, London, Nov. 16, 1912.

Ophthalmia Neonatorum. (Hat die Blennorrhea neonatorum abgenommen?)—C. Crede-Horler. (Zur Technik der Credéschen Blennorrheaprophylaxe.—C. Weidenbaum.
Zentralbl. f. Chir., Nov. 2, 1912.

Ophthalmia Neonatorum, Management of Cases of.—H. McGuire.
West Virginia Med. Jour., November, 1912.

Otitis Media, Suppurative, Importance of Early Recognition of.—P. Hammond.
Boston Med. and Surg. Jour., Nov. 21, 1912.

Tonsillectomy. Too Radical, Some Untoward After-Effects of.—J. A. Stucky.
Laryngoscope, October, 1912.

Tonsillitis, Acute Follicular, with Unusual Sequela, Three Cases of.—S. McCullagh.
Laryngoscope, October, 1912.

Tonsils, Common Varieties of, and Their Recognition.—F. C. Pybus.
Practitioner, London, November, 1912.

Tonsils, Lingual, in Health and Disease.—J. H. Johnson.
Jour. Ophth. and Oto-Laryngol., November, 1912.

THERAPEUTICS

Salvarsan, Administration of, by the Rectum in Children. (L'absorption rectale des arséno-aromatiques chez l'enfant.)—A. J. Weill, Morel and G. Mouriquand.
Bull. Soc. de pédiat., October, 1912.

SURGERY AND ORTHOPEDICS

Ankylosis of the Knee, Operative Treatment of the. (Operative Behandlung von Kniegelensankylosen.)—E. Payr. (Experimentelle Beiträge zur operation Mobilisirung ankylosirter Gelenke.)—M. Sumita.
Arch. f. klin. Chir., Nov. 9, 1912.

Claw-Foot, Operative Treatment of.—J. T. Watkins.
Am. Jour. Orthop. Surg., November, 1912.

Congenital Deformity. (Zur Teratogenie.)—F. A. Kehrer.
Arch. f. Gynäk., Oct. 26, 1912.

Flat-Foot, Traumatic, Treatment of.—A. H. Cilley.
Am. Jour. Orthop. Surg., November, 1912.

Flat-Foot, Treatment of. (Plattfussbehandlung.)—J. A. L. Stephan.
Med. Klin., Nov. 17, 1912.

Lorenz's Operation, Recent Case of, Demonstrating by Roentgen Rays the Development of Acetabulum.—W. S. Haughton.
Brit. Med. Jour., Nov. 16, 1912.

Scoliosis.—A. M. Forbes.
Canada Med. Assn. Jour., November, 1912.

Scoliosis.—E. H. Bradford.
Am. Jour. Orthop. Surg., November, 1912.

Scoliosis (Fixed Type), Treatment of, by Plaster, Supplemented by Pneumatic Pressure.—J. P. Lord.
Am. Jour. Orthop. Surg., November, 1912

Scoliosis, Physiologic.—M. Jansen.
Brit. Med. Jour., Nov. 16, 1912.

Spina Bifida, Old.—E. Tournier and J. Ducuing.
Arch. gén. de chir., October, 1912.

Spondylolisthesis, Traumatic, Following Fracture of a Congenitally Deficient Fifth Lumbar Vertebra.—A. H. Maccordick and J. A. Nutter.
Am. Jour. Orthop. Surg., November, 1912.

MISCELLANEOUS

Anamnesis Questions, Printed, System of, for Children Out-Patients.—F. C. Eve.
Brit. Med. Jour., Nov. 16, 1912.

Child Welfare Work, Trend of Medico-Social Effort in.—W. C. Phillips.
Am. Jour. Pub. Health, November, 1912.

Crippled and Deformed, Industrial Education.—H. W. Orr.
Am. Jour. Orthop. Surg., November, 1912.

Glass Partitions in Children's Ward. (Die Boxstation der Neuen Wiener Kinderklinik.)—C. v. Pirquet.
Ztschr. f. Kinderh., Nov. 16, 1912.

Heat, Stagnation of, as Factor in Infant Mortality. (Die Rolle der Wärmestauung und Exsiccation bei der Intoxication der Säuglinge.)—P. Heim.
Arch. f. Kinderh., Oct. 12, 1912.

Heredity, Recent Research on. (Die neueren Forschungen auf dem Gebiete der Descendenztheorie.)—A. Jacobsohn.
Med. Klin., Nov. 17, 1912.

Infant Mortality, Vaginal Operative Treatment for Uterine Hemorrhage Would Reduce. (Wie können jährlich 50,000 Kinder in Deutschland gerettet werden?)—A. Dührssen.
Berl. klin. Wchnschr., Nov. 4, 1912.

Moist Heat in External Treatment of Infant's Diseases. (La termoterapia nelle malattie dell'infanzia.)—P. Bueri.
Gazz. d. osp., Nov. 17, 1912.

Nurses, Training of, for Sick Infants. (Ausbildung von Säuglings-Krankenpflegerinnen nach einheitlichen Grundsätzen.)—J. Ibrahim.
Deutsch. med. Wchnschr., Nov. 14, 1912.

Race Hygiene Study and Its Importance to Modern Culture.—H. Lundberg.
Jour. Nerv. and Ment. Dis., November, 1912.

Resuscitation, Apparatus for, of the Apparently Drowned or Asphyxiated. (Verfahren für die künstliche Atmung bei Scheintoden und Asphyktischen.)—L. Lewin.
München. med. Wchnschr., Nov. 19, 1912.

School Children, Orthopedic Inspection of. (Prophylaxie des difformités physiques chez les enfants. L'inspection orthopédique scolaire de la ville de Bordeaux.)—E. Kirmisson.
Bull. de l'Acad. de méd., Paris, Nov. 5, 1912.

Shock, Anaphylactic, Salt by the Mouth in Prevention of. (Ueber Schutzwirkung wiederholter Kochsalzgaben per os gegenüber dem anaphlaktischen Schock.)—H. Langer.
München. med. Wchnschr., Nov. 19, 1912.